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NUTRITION IN INFECTIONS*

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CRITICAL EVALUATION OF THE ROLE OF NUTRITION IN THE PROPHYLAXIS AND TREATMENT OF DISEASE

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Whenever significant advances have taken place in a phase of science, it is important periodically to assess critically the degree of accomplishment, to [illegible]

may expose previous overenthusiasm, censure unwarrantable pessimism and clarify new problems that have been created Statistically significant conclusions can be demonstrated after a relatively brief interval with some forms of clinical and basic research Conversely the effects of an experimental maneuver may be so subtle, and may not reach a patent maximum for such a lengthy period of time as to make hazardous the drawing of any early conclusions This situation prevails in nutrition research Premature over optimism with an unrealistic and improper application of some of the recent important advances in the field of nutrition and metabolism has led to some discrediting of the findings among many individuals who otherwise are in the most advantagous position to apply them

Since ancient times it has been suspected that an individual must have adequate nutrition to be well It has been recognized, to a lesser extent, that the wel[illegible]
is only
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food nutrition, and metabolism that a scientific foundation for many empirical beliefs has been constructed Biochemists physiologists physicians micro biologists nutritionists veterinarians, food technologists and other specialists have contributed to these studies The vast amount of accumulated data has led to much confusion with conflicting opinions and interpretation of the data Perhaps nowhere in the realm of biology has there been gathered such a mass of facts that needs to be correlated and systematized as in the field of nutrition

A considered review of much of the pertinent published data indicates that no reasonable doubt can be entertained regarding the catholic role performed by nutrition in the maintenance of a positive state of high grade health and in the prophylaxis and therapy of disease The nutrients supplied to the tissues exert powerful direct influences not only as structural essentials for synthetic processes but as regulators of all those biochemical processes that constitute the sum total of body metabolism The ability of a patient to recover from an illness injury or operation is closely related to his previous and current nutrient supply Rare indeed is the patient who cannot be aided by proper nutritional guidance since nutrition is probably the most important environ mental factor affecting health and disease

Some of the recent and current research that forms the basis for these conclusions is reported elsewhere in this monograph by the original investigators As it is impossible in the brief space allotted to me to discuss more than a limited phase of this vast subject only certain salient areas in the forest of nutrition will be explored in this presentation, and some of the major problems relevant to the role of nutrition in the prevention and treatment of disease will be underscored

Developments in Nutrition Research

The infinite number of factors involved in metabolism makes research in this field, of necessity, very difficult to evaluate The number of permutations and combinations of biochemical reactions feasible from the known intermediary chemical metabolites is almost beyond calculation In the neophyte stages of our knowledge of metabolism, it was considered that the metabolic pathwa of protein, carbohydrate, and fat metabolism were separate and distinct I the present adolescent stage of our knowledge, we know that this is not true Studies using compounds labeled with radioactive elements have proved conclusively that the intermediary pathways of metabolism for carbohydrates, protein, and fat frequently merge for several steps and cross at numerous intersections The vitamins and minerals acting on numerous enzymatic and synthetic processes may act through their adequacy or insufficiency as red or green lights all along the metabolic roadway

Evaluation of basic research in nutrition is quite complex because, in the evolution of a problem, one laboratory often fails to duplicate the findings of another Reported results of nutrition and metabolic studies by different research teams may even be contradictory Multiple factors influence the apparent mechanism of action of a compound and the alterations produced by a deficiency These factors include differences in the management of animals or handling of tissues, small variations in other seemingly unimportant or unrelated nutrients, a divergency in type of tissue, organ, or organ system studied, and a different experimental approach

The external conditions influencing clinical research are even more numerous than with basic research When determining the effects of experimental deficiencies, for example, it must be ascertained whether any associated insufficiency is present, whether all other environmental factors have been excluded is a cause of observed results, and whether abnormalities detected are primary r secondary The latter pitfall is illustrated by the macrocytic anemia of corbic acid deficiency in infants This condition responds to either folic d or ascorbic acid, the hematopoietic defect in this case apparently being to a conditioned folic acid deficiency, for ascorbic acid appears to be necessary for the conversion of folic acid to its active form, folinic acid

When determining the positive results consequent to administering nutrients to healthy men, deficient humans, or sick individuals, psychologic influences that subjectively bias the patient or observer must be ruled out Whenever possible, the double blind test method should be used In this plan of investigation, neither the patient nor the observer knows which medication is the nutrient element or combination and which is a placebo Overenthusiasm,

with an expectation of beneficial effects from a compound, as well as pre existing prejudices thus are ruled out as factors influencing the interpretation of clinical signs and symptoms

There are ample critical, statistically significant experimental studies to indicate that good nutrition is important for optimal resistance to infection, for a superior tissue capability to cope with disease and injury, and for maximum antibody production Good nutrition will help to insure rapid wound healing after surgery, burns, or radiation exposure Normal blood protein levels, osmotic pressure, and normal hematopoiesis will be maintained Adequate nutrition will sustain tissue synthetic processes, secure correct hormone and enzyme activity and enable the liver and gastrointestinal tract, cardiovascular apparatus, nervous and other organ systems to function normally Proper nutrition thus is not only important in preventing weight disturbances and specific deficiency disease, but it has an equally vital role in maintaining high grade health Thus, in a nonspecific manner nutrition participates in the prophylaxis against most acute infections and when used as an adjuvant n therapy, shortens the duration of convalescence of virtually all pathologic rocesses The term high grade health" is frequently used in this discussion r it seems quite clear that, even in the absence of all manifest disease, there are still varying levels of health

The components of a good diet are well known There must be a sufficiency of calories, of proteins, especially animal proteins and of vitamins and minerals, including the electrolytes Therapeutic diets for acute infections and other diseases are extensions of the normal diet They not only must maintain the normal nutritional requirements but must provide for increased physiological requirements for certain nutrients and increased losses of other nutrients occasioned by the illness as well as for the replacement of any previous depletions The requirements of each specific nutrient should be estimated separately for the ill individual The total nutrient needs also will vary from patient to patient

In general, an attempt should be made to supply all necessary nutrients through the diet In major illness, marked metabolic alterations may be produced by physiological and psychological stresses, losses of nutrients from the body may be unduly large, and intake may be poor This will produce rapid nutritional deficiency, which will be especially severe if there were preexisting depletions It is far more difficult to correct nutritional deficiency than to prevent it In an attempt to meet the nutritional demands of the ill individual, pharmaceutical preparations such as vitamin capsules and caloric concentrates are of great aid to the physician In the occasional case where all requirements cannot be met by the oral route, parenteral alimentation may be administered

There is no substitute for clinical acumen to insure the proper application of nutrition therapy It is unfortunate that too many people have the impression that the benefits of nutrition therapy can be accomplished through a mass' effect by dumping into an individual the maximum possible amount of every known nutrient In an attempt to do this attention may be focused on purified crystalline compounds and thus be diverted from the total diet

and nutrition of the patient There are so many unknowns in nutrition and metabolism that the focal aim of nutrition must be to supply a wholesome diet to insure an adequate supply of all known and unknown factors Supplemental vitamin capsules, for example, are unquestionably an important and essential adjuvant to nutrition therapy, but it always must be remembered that they still are only a reenforcement for the diet and not a substitute

New problems have been created by the injudicious application of nutrition therapy Any mode of treatment, any
to the body, may act as a two edged swo
benefits may be wrought Administe
may be produced Such is the case
harm, several factors should be considered when planning a diet regimen These are

(1) The relation of nutrients to pharmacological agents The title of this paper reasonably could be extended to read "evaluation of the role of nutrition in the prevention and treatment of disease and in the prevention and treatment of the complications of pharmacological therapy "

(2) The relation of nutrients to both the disease state and the stage of the disease process The nutrient element that is so beneficial in one phase of an illness, can adversely affect, in the very same dosage, the internal milieu of the body in another phase and produce toxic manifestations and death

(3) The potentialities for toxicity of the nutrient element *per se* Nutrients cannot be administered with complete impunity, even to normal persons Some elements essential for life may, in excess, produce severe tissue damage

(4) The relation of the various nutrients to each other For an optimal effect, there must be a proper balance and proportion among nutrients and *all the nutrients utilized by the tissues must be simultaneously available to* the cell This holds true whether the nutrient be classified as essential because the body cannot manufacture it, in which case it must be supplied from *exogenous sources, or whether*
the cell can produce it in the
in anabolic processes, more fre
essential elements

The Relation of Nutrition to Pharmacological Agents

The recent introduction of numerous new pharmacologic agents has made the problem of nutritional therapy more complex As examples of the manner in which pharmacologic agents superimpose additional dietary requirements
r se, diuretic drugs, antibiotics, hormonal
ed
used include various oral and parenteral
mercurial compounds, carbonic anhydrase inhibitors (Diamox), and ion exchange resins They either decrease sodium retention by the kidney with increased excretion of sodium in the urine (mercury, Diamox) or they may prevent intestinal absorption (ion exchange resins) and thus increase fecal losses of sodium Sodium chloride must be carefully adjusted in the diet Most patients requiring diuretics will benefit by a sodium restricted diet A

low sodium syndrome, which is occasionally fatal, may ensue when massive diuresis with large losses of sodium is produced in a patient on a diet markedly restricted in sodium This syndrome is corrected by replacing the depleted electrolytes

The water soluble vitamins also are lost in abnormal amounts from the body during a huge diuresis This loss may be superimposed upon some previous nutritional depletion that many patients have while receiving diuretics, because of an anorexia associated with their infirmity and often increased by a tasteless diet Some of the vague symptoms following frequent diuresis may be alleviated by administering large supplements of the water soluble vitamins

Oral antibiotics now are prescribed universally for the treatment of many infections Infections raise the requirements for most nutrients because of the increased metabolic rate secondary to fever and toxicity and the physiologic changes produced in the tissues by the stress of the disease When nausea, vomiting, diarrhea and excessive sweating accompany the infection there are additional losses that must be compensated Anorexia may compound the difficulties Antibiotics often aggravate this deleterious state Some oral antibiotics and chemotherapeutic agents produce anorexia A gastro-intestinal upset manifested by vomiting and diarrhea occurs in as many as 25 per cent of patients receiving chlortetracycline and oxytetracycline The broad spectrum antibiotics destroy the normal bacterial flora of the intestinal tract The biosynthesis of vitamins in the intestine normally is a fairly considerable source of many B complex vitamins and of vitamin K The normal bacterial flora also may be required for the utilization of some vitamins Sterilization of the intestines by antibiotics increases the need for an exogenous source of vitamins It may be a factor in precipitating signs and symptoms of acute vitamin deficiency in subjects with infection All patients with infection require nutritional support Additional care must be exercised when ral broad spectrum antibiotics are being administered to them These atients would probably benefit from a vitamin supplement containing the complex factors, perhaps vitamin K and also vitamin C, for which there a notably increased demand in situations of stress Recently a combination of an antibiotic with these vitamins has been prepared in a single capsule This would appear to assure an adequate intake of those vitamins that are especially needed in stress situations under treatment with antibiotics and may reduce the number of individuals who have a delayed convalescence or other complication caused by nutritional inadequacy

Cortisone and related compounds The subject of the interrelation of hormones nutritional elements and enzymes is a broad and fascinating one that in itself could be the basis for a monograph Cortisone and related compounds are now being very widely used by physicians for the treatment of rheumatoid arthritis rheumatic fever and other so called collagenous diseases and for many serious allergic disorders Nutritional regulation has been very important in preventing and treating complications of cortisone hydrocortisone, and adrenocorticotropic hormone These compounds have in common their ability to cause a retention of sodium and chloride with a concomitant increase in weight and development of tissue edema a loss of potassium with the

possible consequences of severe hypopotassemia, a rise in blood pH, a protein catabolic response with negative nitrogen balance and possible tissue wasting and increased glycogenesis with the development of hyperglycemia and glycosuria The incidence of these deleterious side effects is related to dosage, to treatment of the disease process, to previous nutritional status, and to current nutritional intake Dietary regulation has minimized the consequences of these side effects Weight gain and edema are decreased by restricting sodium intake Hypopotassemia is overcome by encouraging the intake of fruit juices and other foods high in potassium and possibly by potassium supplements The deleterious effects of negative nitrogen balance are counter acted by a high protein diet Adjusting the percentage of carbohydrate and the total caloric intake may control hyperglycemia if it appears

A new synthetic derivative of cortisone, prednisone (metacortandracin, meticorten), though three to five times more effective as an anti inflammatory agent than cortisone or hydrocortisone, has only a slight effect on the serum electrolytes The need for sodium restriction and potassium supplementation is therefore not required to the same degree as with the other corticosteroids Preliminary studies have indicated that the protein catabolic response is equally great and that negative nitrogen balance may be even more marked with prednisone than with the other compounds Adequate protein intake must be assured with all corticosteroids to prevent the deleterious consequences of protein disequilibrium

Isoniazid Pyridoxine administration prevents the toxic effects of isoniazid which is used routinely at present in the treatment of tuberculosis Isoniazid adversely effects pyridoxine metabolism, as it forms a conjugate with the vitamin resulting in its inactivation and excretion Pyridoxine deficiency with neuritis develops If large doses of pyridoxine are given with isoniazid, no neuritic symptoms occur Once neuritis has developed, however, it is necessary to discontinue the isoniazid in order to produce a remission

Relation of Dietary Requirements to Disease Stage

Each disease affects the requirements for nutrients to a different extent In many illnesses, the stage of the disease also has a profound influence on dietary requirements

As examples of the varying requirements of different diseases, ulcerative colitis, diabetes and congestive heart failure will be briefly discussed In *ulcerative colitis*, tremendous amounts of all nutrients are lost through the colon, thus causing a severe metabolic disturbance Fluid electrolytes, vitamins, and other nutrients are dissipated The problem of nutrition is rendered more difficult because food may not be retained in the intestinal tract for a sufficient length of time to permit its absorption There is usually an associated anorexia, and bland, low residue diets have to be continued for long periods of time In these patients, many serious complications can be

needed if there is a severe anemia Pellagrous tongues are not infrequent

because of poor absorption of vitamins Parenteral vitamin therapy may be indicated

In *diabetes*, total calories are regulated upward or downward to achieve a normal weight The total amount of carbohydrate is regulated, as well as its distribution during the day, in order to prevent postprandial hyperglycemia The diet is coordinated with the type and amount of insulin administered In decompensated diabetes, there is a negative nitrogen balance and fluid, electrolyte, and vitamin losses Fluids sodium chloride insulin, and, at times, potassium will be required to restore compensation High protein and high vitamin diets should be continued for some time following acute episodes to replace the depletions

Many researchers believe that a large number of the signs and symptoms of *congestive heart failure*, whatever the underlying pathology, are due to the failure of the kidneys to excrete sodium in normal amounts In order to over come the deleterious affects of this sodium retention, it is necessary to place these patients on a sodium-restricted diet Though there may be a somewhat restricted choice of foods, and flavoring must be accomplished without salt, it is rarely necessary to deviate greatly from the normal dietary pattern The nutritional deficiencies seen in patients with heart failure who are at home, arise rather frequently because the patient has not been told what foods he

apeutic diet The importance of a high protein diet in the therapy of *liver disease* is now universally accepted Many clinical studies have confirmed the beneficial achievements from this therapy Experimental liver disease is more readily induced when the diet is deficient in proteins Liver disease is associated with several abnormalities in protein metabolism Some patients with chronic liver disease are sensitive to high protein diets If such diets are used indiscriminately, hepatic coma may be initiated In the presence of hepatic coma, protein restriction must be practiced An attempt to force a high protein diet may provoke a premature fatality among such patients Fat is not so harmful in liver disease as it was once believed to be Adequate caloric, protein, vitamin, and mineral nutrition is much easier to achieve if some fat is allowed

Similar problems are present in treating *kidney disease* During the stage of massive proteinuria, protein intake may have to be doubled On the con trary, in the presence of renal failure with uremia, the protein intakes should be reduced to the basic minimum In renal disease with edema, sodium restriction is necessary If a ' sodium losing ' nephritis is present, high sodium intakes are to be encouraged When the kidney is losing potassium, potassium replacement is necessary to prevent further kidney damage from hypopotas semia Conversely, in azotemia from acute anuria or chronic renal damage, hyperpotassemia may be the problem

It may be appropriate at this time to note the influence exerted by the caloric content of the diet on the requirements of many vitamins, especially those of the B complex The requirements for some of these vitamins are minimal

when caloric intake is greatly restricted It is rare to see manifest vitamin deficiency disease in total starvation During refeeding after a period of starvation overt vitamin deficiencies have been precipitated when the vitamin allowances were not increased sufficiently to meet the increased metabolic demands of the high caloric schedule

Toxicity of Nutrient Elements

Certain nutrients in excess can be toxic Continuous vitamin A administration in high levels may produce multiple severe toxic symptoms especially in infants In *hypervitaminosis A*, there is an elevated concentration of vitamin A and alkaline phosphatase in the serum X rays of the long bones show a characteristic shell like bony hyperostosis An excess of vitamin A, as well as an absence of vitamin A in the feedings of pregnant rats will result in congenital anomalies in the offspring It is seen thus that deficiency or excess of the same substance cause major clinical and experimental abnormalities

A prolonged greatly excessive intake of vitamin D will produce toxicity In *hypervitaminosis D* anorexia nausea, vomiting diarrhea, weakness, headache drowsiness, dnd weight loss may occur Such genitourinary symptoms as polyuria nocturia and dysuria associated with metastatic renal calcification may characterize the syndrome X rays also may reveal calcification of vascular organs and the prostate Laboratory studies show an elevated serum calcium concentration, proteinuria elevated blood urea nitrogen and other evidences of impaired renal function

Both vitamin A and vitamin D toxicity syndromes are reversible, and they are cured by eliminating the supplementary vitamin

Another potential danger of prolonged excessive intakes of a nutrient supplement lies in the possibility that the cells may accommodate themselves to the nutrient and then require the large amounts for normal function This phenomenon has been demonstrated repeatedly in microorganisms and is a basis of bacterial resistance to antibiotics Cases of a typical pyridoxine deficiency syndrome in infants precipitated by withdrawing large amounts of supplemental pyridoxine have been reported recently Restoring the large doses of the vitamin alleviated the symptoms It was then necessary to wean the infants away from these excessive supplements

Obesity also may be classified as an example of the deleterious results of overnutrition In caloric insufficiency, functional impairments of the organs develop, the normal course of metabolic processes are interfered with, and the body in general deteriorates Anatomical changes will occur in most tissues if the deficiency of calories is severe and prolonged Resistance to infection is markedly lowered and healing proceeds with difficulty Similarly, functional and anatomical disturbances also are induced by a caloric overabundance Obese individuals are more prone to develop degenerative cardiovascular diseases osteoarthritis diabetes, and other metabolic disorders They often handle infections less well, have a lower endurance, and are greater operative risks than people of normal weight Obesity frequently results from the ingestion of naked calories *i e* foods devoid of other dietary essentials It is

not at all unusual to discover among the obese signs and symptoms of vitamin protein and other malnutrition that require active correction during the course of a reducing regimen

Interrelationship among Nutrient Elements

About 50 purified nutrients are acknowledged today as indispensable for growth and development These include amino acids minerals vitamins fatty acids total calories and water Strong interrelationships exist among these dietary essentials For the most efficient utilization of any one dietary substance all metabolically related factors must be present simultaneously Failure to appreciate fully the necessity for the coinstantaneous presentation of nutrients to the cells has been responsible for some reported achievements ... h
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u ... adequate protein supplies and ... july atomic radiation ... ess and rapid tissue catabolic state that accompanies severe acute illnesses and burns are contingent nitrogen balance may occur on a diet which would be more than adequate during health The restoration of protein anabolism with a positive nitrogen balance requires astute attention to nutrition for the construction of proteins can proceed only when all component parts of the molecules being elaborated are available simultaneously An incomplete amino acid mixture cannot be utilized for the production of intermediary compounds of protein anabolism and will not be retained by the organism If all the amino acids necessary for protein synthesis are not present production at that moment is limited by the one least available Amino acids not utilized immediately for protein construction are lost for this purpose They enter the general metabolic pool and may be utilized in the production of other nitrogenous substances or else may be irreversibly further metabolized Two nutritionally incomplete foods or artificial mixtures supplement each other only when administered together

Carbohydrates and fats have both a specific and nonspecific regulatory effect on protein metabolism It is difficult to produce a positive nitrogen balance with insufficient calories though increasing the caloric intake above a critical level does not further promote the utilization of an adequate amount of protein When carbohydrates are fed simultaneously with proteins dietary amino acids are maximally utilized for protein synthesis ... is no need for the protein com... pool to be used as a source of ... f carbohydrate metabolism ... formation of nonessential a... acids Experimental animals consuming a ... precursors for the virtually fat free diet have a decreased nitrogen balance and excrete significantly larger quantities of certain amino acids in both the urine and feces than animals on an isocaloric diet with average proportions of fat

There is an increased demand for mineral elements during periods of protein

anabolism, for potassium, sulfur, and phosphorus are laid down with nitrogen in the formation of tissue protoplasm The effectiveness of a high protein diet may be decreased by an insufficiency of mineral substances

Normal protein metabolism also requires liberal quantities of vitamins, especially those of the B complex and ascorbic acid The vitamins act as biocatalysts in both synthetic and oxidative reactions Riboflavin is retained with protein, while negative nitrogen balance is accompanied by a negative riboflavin balance The poor wound healing and decreased rate of growth in experimental ariboflavinosis actually may be reflections of the injurious effect of riboflavin deficiency on protein metabolism The essential amino acid

amino acid decarboxylases and is involved in protoporphyrin, antibody, and other protein synthetic processes Pantothenic acid is a component of co enzymes A, which is involved in the acetylation processes of intermediary protein metabolism Vitamin B_{12} has a specific role in nucleic acid and porphyrin synthesis, and will increase the utilization of marginal quality pro teins Cyanocobalamin and choline both function in the methylation process and spare the essential amino acid methionine Ascorbic acid is related to the metabolism of the amino acids tyrosine and phenylalanine The hepatic storage of complexes containing folic acid, riboflavin, niacin, biotin, and pantothenic acid parallels the level of dietary protein Lastly, there is evidence that both ascorbic acid and pantothenic acid may indirectly influence protein metabolism through their effect on the adrenal cortex and their relationship to the secretion of adrenal cortical hormones

In summary, it is apparent that protein metabolism is influenced by the total composition of the diet Virtually every element of nutrition has a role in assuring protein equilibriums that are favorable for the prophylaxis and treatment of disease The simultaneous presence of a sufficient amount of complete quality proteins, of carbohydrates, fats, and total calories, of minerals and of vitamins is needed if every phase of the metabolism of each individual dietary component is to proceed compatibly toward maximum health

Problems of Vitamin Therapy

Even when all those working in the field of clinical nutrition have agreed that a vitamin supplement is indicated for a specific situation, there has been great difficulty in determining the qualitative and quantitative composition of the preparations Some clarification is now possible concerning this problem of vitamin therapy

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vitamin K in terminal pregnancy or in the newborn infant, vitamin A in treating nyctalopia or follicular hyperkeratosis, and vitamin B_{12} in pernicious

anemia There are numerous interrelationships between the vitamins One vitamin may promote the conversion of another vitamin into its active form or it may protect other vitamins from oxidative destruction The metabolism of a specific vitamin is often greatly influenced by the adequacy of others in the diet Several vitamins often catalyze the same metabolic reactions Successful dietary management requires that the presence of all vitamins be assured

There is a close association of many of the vitamins in natural foods In general, when a diet is deficient in one element, it will be found wanting in others It behooves the physician to prescribe a multiple vitamin preparation whether vitamins are administered for prophylaxis or for therapy Many commercial therapeutic vitamin preparations are lacking in pantothenic acid, [illegible] of other vitamins, and all play a cogent role in certain specialized tissue functions such as hematopoiesis, antibody synthesis, and corticosteroid hormone secretion It would seem logical that those chemicals, which are present in virtually all body tissues and are involved in a vast number of critical biochemical reactions, should be incorporated whenever supplemental vitamins are indicated, even though a recommended daily allowance for them has not been ascertained While we await further increments of our knowledge concerning those recently characterized vitamins, it probably is best, at the present time, to follow the tentative recommendations of the Committee on Therapeutic Nutrition of the National Research Council, Washington, D C, concerning the qualitative and quantitative composition of vitamin preparations Because of the difficulty in ascertaining the essentiality and quantitative needs of vitamin substances, supplements must never be a substitute for a wholesome diet with its content of known and perhaps as yet unknown factors

Iatrogenic malnutrition induced in a patient by a poorly conceived therapeutic diet has been observed with an alarming frequency So called therapeutic diets at times contain inadequate amounts of individual nutrients even for the normal body and, in addition, they frequently neglect the superimposed demands of the disease process Iatrogenic malnutrition thus can be classified as a combination of primary and secondary malnutrition

Therapeutic diets formulated especially for the treatment of particular signs or symptoms of a disease are most often lacking in total nutritional adequacy The most frequently inadequate nutrient is protein The demands for protein commonly are not met in patients with ulcerative colitis and other diarrheal diseases, in diets for peptic ulcer, especially during exacerbations, in kidney diseases associated with massive proteinuria, and in diets for cirrhosis and hepatitis Diets for peptic ulcer usually are unduly low in calories and markedly deficient in ascorbic acid In general, soft, liquid, and bland diets and postoperative regimens are apt to be nutritionally inadequate in vitamins, proteins, and calories Minute attention should be paid to special diets, for tissue nutritional depletion is readily prevented but often difficult

choosing foods Education of the public, pointing out clearly what foods should be eaten and emphasizing the essential role of nutrition in the prophylaxis and therapy of disease, is necessary to increase the percentage of well nourished individuals in the population and thus to maintain our nation in maximum productivity

Summary and conclusions

The nutrient supply to the body unquestionably exerts direct and powerful influences upon all the biochemical processes that constitute the sum total of body metabolism All research confirms that nutrition and health are in separable Overnutrition undernutrition, or an improper balance of the nu trient elements of the diet all have a detrimental effect Strong interrelations exist between dietary essentials The simultaneous presence of all nutrients is required for maximum tissue growth and synthesis

Nutritional therapy is frequently of primary importance in the treatment of

may be acclerated or retarded as a result of the diet pattern Nutritional ther apy, whether by diet alone or in conjunction with special pharmacological supplements must be correlated with other specific and nonspecific therapy of the illness The phase of the disease and the nature of specific tissue and organ pathology must be delineated in order that the potentialities and limitations of therapeutic nutrition may be recognized Modern techniques, procedures, and preparations require responsible application

Most therapeutic nutritional regimens should be extensions and modifications of the normal Some new diets purported to prevent certain chronic illnesses

of our scientific discoveries Extensive research is still necessary in the fields of nutrition and metabolism if the full potentialities of lifelong nutritional guid ance are to be achieved The proper utilization of knowledge already gained requires perspicacity, good judgment clinical acumen, and a thorough under standing of the principles of nutrition

Discussion of the Paper

PROFESSOR FRANCISCO GRANDE (*University of Saragossa Medical School Saragossa, Spain*) It will be difficult for me to discuss at length the paper by Doctor Halpern because it has touched on so many problems This paper has given us such a clear idea of the present situation of nutrition that I do not think it is worth spending your time in discussing its general outlook, with which I am completely in agreement I believe however, that it may be worthwhile to take a few points in particular and to try and view them from a somewhat different angle especially on the basis of my own personal ex perience

I am more interested in the public health point of view than in the clinical treatment of diseases I think we can discuss some of the problems of nutrition diseases from the point of view of prophylaxis If we know the role of an agent in the production of disease we are in a very good position for taking prophy lactic measures against the particular disease In the case of nutritional dis eases we can do very much nowadays in the matter of prophylaxis I believe that an analysis of our potentialities in relation to the prophylaxis of nutritional diseases is worth considering

We can classify diseases that we usually call nutritional—that is produced by changes of dietary origin—into four groups We have first of all a group of diseases which are produced by dietary deficit by lack of nutrients We may call them *deficiency diseases or diseases of malnutrition* if you like

We have a second group which will be produced by disturbances in the normal proportion of the different nutrients that is imbalances

Other kinds of nutritional diseases can be produced by overfeeding by ex cess of total amount of food or of some of the elements in the food We can call those diseases of overfeeding

Finally we have another group of diseases which we may call toxic ones re sulting from the fact that foodstuffs may be toxic or may contain some toxic substances So we call these effects toxic effects and we may d scuss this prob lem a little more fully later

Regarding the deficiency diseases I believe you will all agree that our situ ation today is quite satisfactory Our theoretical knowledge suffices I believe to eradicate most of the deficiency diseases if we have the economic and opera tional means to do so In other words we know enough to prevent scurvy to prevent beriberi If we are not able to do that it does not depend upon lack of knowledge but upon the pure operational or economic difficulties There fore I think that our point of view as to the prophylaxis of deficiency diseases is completely sound and needs no more discussion

The same may be true in the case of the imbalances those diseases—pellagra for instance—which are produced by alteration in the normal composition of the diet We know enough about the alterations of the diet that produce these diseases and therefore if we have the material means of changing or avoiding these alterations we can avoid the disease

The problem of overfeeding is now attracting great interest in the world in some countries at least The problem of nutrition in the world at large is a problem of underfeed ng The great majority of the human race is of course ur derfed But there are countries in the world—the United States of course is a case—in which overfeeding may be a problem and we begin to realize now that overfeeding can also be a medical problem and that a decrease of the amount of food that we are using may be important in the prevention of some types of diseases You know as Doctor Halpern mentioned that our group in Minneapolis is interested in this problem and in the relationship between the blood cholesterol and the diet The relation between blood cholesterol and the incidence of coronary scleros s has been demonstrated At least Doctor Keyes has collected a lot of evidence in this direction I am not in a position to dis cuss the question of whether high cholesterol is the cause of arteriosclerosis I

know that an increase of fat in the diet produces change in the blood cholesterol This is more important than the cholesterol content of the diet, as Doctor Halpern himself has already observed

Of course the obvious prophylaxis of this type of disease—if it is shown that the high fat content of the diet produces high blood cholesterol and that high blood cholesterol produces arteriosclerosis—will be to decrease the amount of fat in the diet So the theoretical basis is clear, provided we supply the clear cut evidence

My main interest will be to discuss the so-called toxic effect of diet, because I believe that insufficient attention has been paid to this problem I think we may distinguish three kinds of toxic foods First, toxicity may result from contamination and this is a problem of sanitation, which I am not going to discuss The second type of toxins are those already existing in the foodstuffs These we may call the natural toxins Finally, there are the toxins produced in the foods by handling by the processing of foods during industrial and technological maneuvers These toxins are not produced naturally

Of the natural toxins, we have a very nice, interesting example in the disease which you know as lathyrism For many years it has been known that the consumption in great amount of this leguminous seed, *Lathyrus cicera*, produces a characteristic difficulty of the nervous system called lathyrism, which is in short a spastic paralysis, from degeneration of the tract It has been impos

sweet pea whose flower you know—which produce in rats a very typical picture This picture, however, is a bone disease, with changes in the phosphatase of blood It has nothing to do with the human picture of lathyrism Therefore you have two seeds used as food that contain toxic substances producing very characteristic but *different clinical pictures in man and in animals* It may be that foodstuffs contain many other substances which are able to produce toxic effects in the human body If, in the future, our knowledge progresses in this direction there is no reason why other substances that we are using today as foods may not also be found to contain similar things that may be the cause of some of the diseases for which we have no explanation today

Of course, the prophylaxis of this type of disease is very simple if we know exactly the relationship between the particular foodstuff and the disease In the case of lathyrism it has been enough in my own experience in Spain to

ment on It may be that

not related somehow to the existence of toxic substances in the natural food stuffs

The next problem that I should like to discuss in connection with the toxic

effects of foodstuffs is that of toxins produced by handling by the processing of foods You all are familiar, I am sure with the effects of the bleaching of flour You know that certain chemical changes occurring during processing produce in the dog a condition characterized by running fits I wonder whether by similar chemical action on natural foodstuffs we are not also producing changes in other nutrients which may eventually lead to noxious effects in the human body

We are concerned here chiefly with the problem of the relationship between nutrition and infection To put it better nutrition is important in the prophylaxis not only of the poorly named nutritional diseases but also of other kinds of disease Doctor Halpern has made clear the point that everything happening *in the body is dependent upon the nutritional situation of the body* Therefore it is not necessary for me to go into more detail to convince you that nutrition is important for everything including infection Unfortunately we don t know much about the relationship about the mechanism of the relationship between infection and nutrition In fact all our observations still lack scientific evidence

I recall that during the Spanish Civil War I was very interested in trying to find out the relationship between for instance the increase of certain forms of clinical tuberculosis or the increase in cases of malaria and the nutritional situation of the population I collected much information but when I sat down and tried to put it into figures and to make a statistical analysis of the results I always found that my information was not sufficient to make such an appraisal of the relation That is what is happening with much of our present knowledge in this regard

If you take one of the classical books on nutrition the book by Doctor Jolliffe for instance you can find in two different chapters—the chapter by Doctor Keyes and the chapter by the late Doctor Tisdall—two different opinions as to the relationship between the diet and the problem of infection Therefore I believe that it is one of the fields in which our knowledge has to be expanded We need to look for the basic facts about the relationship between the two processes of infection and nutrition

It has been claimed that the infection or rather the response of the human body to infection is a problem of protein nutrition After all the formation of antibodies is protein synthesis and it forms a part of protein metabolism The problem is not so simple as that You may have changes in one direction in the formation of antibodies and changes in another direction in the behavior of that particular disease in the clinical development of the disease Therefore I believe it is fair to say that we still need a lot of basic work in this field of the relationship between the infection and the nutritional situation of the host But there are still other problems in connection with infectious diseases that I suppose must also be investigated and that I am sure will give important information for the future

A few months ago Doctor DuBois of the Institute was in Minneapolis discussing the present situation of infectious diseases He gave what I thought was a wonderful address He pointed out a series of facts that for me were

certainly interesting He pointed out that with the use of antibiotics we nearly have won what we may call the war against bacteria We have put a lethal end to infection We have not prevented infection Besides, we are mainly in the fight with bacteria We have saprophytes living in our body Some are doing things which are useful for us Some may also be producing substances of the nature of those toxins which may be harmful to our body and may also be interfering with the host's nutritional processes

The same thing happens with so called latent infection It is difficult to explain why, at one moment, a man who has been carrying some latent infection without consequence suddenly develops the clinical symptoms of the disease Is that related to some change in the chemical processes in the body? Is it related to some change in the nutritional situation of the man? I believe this cold war against the bacteria is still to be won and that a lot of progress will take place if we know better which of the effects of these latent infections are an effect of the saprophytes on the nutritional processes of the body Therefore, our problem in dealing with the relationship between infection and nutrition is two fold On the one hand, we must start to study the actual process of infection On the other hand, we have to pay attention to the fact that infection is not the only thing that bacteria and other germs cause in the body, but that there may be important effects other than just the classical well known effects of infection

IMPLICATIONS OF OBSERVATIONS MADE DURING EXPERIMENTAL DEFICIENCIES IN MAN*

By M. K. Horwitt

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For the past 14 years, the Biochemical Research Laboratory of the Elgin State Hospital, working under the sponsorship of the Food and Nutrition Board of the National Research Council, Washington, D. C., has been engaged in evaluations of the nutritional requirements of man in an effort to obtain basic information that could be related to physical and mental health. In these investigations, 10 to 15 subjects were maintained for approximately 2 years on specially controlled dietary regimens partially depleted in a single nutrient [illegible] the same controlled [illegible]

on infection and on other stresses as during the course of each experiment there were the usual number of intercurrent disorders and traumatic experiences that might normally be expected in 30 subjects over a 2 year period. Attempts to evaluate the course of intercurrent infections and of one epidemic of a gastrointestinal disorder that required the use of sulfasuxidine gave data which were inconclusive. Since it is not possible to relate the course of most infections with a given nutritional state, the quantitation of an infectious state is difficult. In the absence of specific data obtained from experiments specially designed for the study of infection, this presentation may be a bit more philosophical than most. After 25 years of rather intensive personal application attempting to *obtain a better understanding of the science of nutrition, however, perhaps* you will forgive me if I present an interpretive paper.

A few years ago,[1,2] as a consequence of observations made during our studies of riboflavin deficiencies in man, we proposed the somewhat oversimplified theory that some lesions of nutritional deficiency that we see in the adult are a consequence of the retardation of normal tissue replacement and repair or, in other words, the retardation of local growth. This generalization is based not only on the well known inhibition of the growth phenomena in young animals on suboptimum diets but also on the realization, which has been fortified by recent studies with isotopes on the turnover of tissue components, that the formation of new tissue components is almost as rapid in adult life as in the very young. This simple statement was offered as a substitute for more complex explanations for the lesions of certain vitamin deficiencies. Though the term growth is usually reserved for changes that we can see or weigh, it is not inconsistent to consider the replacement of worn-out metabolic systems or of tissues damaged by the stresses of one's environment or activity as part of the general phenomenon of growth. Both involve the same fundamental process, the formation of new cells.

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If one thinks of infection as a type of environmental stress in which tissues may be destroyed by the ravages of an infectious agent or against which spe cific defenses such as antibodies and leucocytes must be manufactured it is not difficult to understand why the common nutrilites have been given so much at tention in research on infection Unfortunately the general value of the thesis that good health and good nutrition are synonymous has led some to reach for interpretations of experimental data that may not be justified and as a conse quence the critics of vitamin prophylaxis and realimentation have had some specific things to criticize Though millions are spent with considerable fan fare in an effort to prevent the rare but more spectacular diseases attempts to achieve a sane level of nutritional prophylaxis have been given the well known jaundiced eye The blame for this apparent discrepancy in public health edu cation may be an indirect consequence of the activities of a minority who have oversold the vitamins for selfish reasons but all too often the misguided judg ment of sincere men has also led us astray

Perhaps the most significant error made in nutritional research is in the use of an experimental plan in which one studies the effects of the total withdrawal of a nutrilite from the diet of a fast growing animal without giving simultan eous attention to the effects of partial withdrawal By definition a nutrilite is a compound that the body cannot synthesize and is essential for the main tenance of the integrity of the living cell The complete withdrawal of this compound produces a kind of total deficiency and debility due to a combina tion of many primary and secondary effects that are not noted when the nutrilite in question is given to the animal in normal amounts

Although many important scientific leads have come from total withdrawal experiments and though many investigators must be conscious of the need for grading the severity of a depletion study this technique of setting up a straw man to be knocked down with ease has now jumped the borders of pure nutri

for reproduction

tory experiments so that we can advance more quickly our knowledge of the

pair fed litter mate unless the intermediate levels of the deficiency in question are included in the experiment

One of the complications of controlled research on the course of human disease that may be pertinent to the subject of this monograph is the effect of bed rest

on the vitamin depleted patient It is now generally recognized that a patient immobilized in bed for a period of time tends to go into negative nitrogen balance[3, 4, 5] This is apparently true even though no acute infection or fever is present and when bed rest is prolonged the muscle atrophy which takes place becomes obvious The striking cure of the early stages of pellagra when a patient is placed in bed without supplementary therapy has been noted frequently and, in the light of our present knowledge of the curative effects of tryptophan this is no longer the surprise it might have been What better source of tryptophan and niacin than one s own flesh?

Of some interest in this regard is the effects of bed rest on volunteers with experimental thiamine deficiency About 10 years ago[6] during studies on thiamine requirements of man 3 out of 11 subjects were confined to bed for extended periods as a precautionary measure following the appearance of neurological signs of thiamine deficiency In these subjects the lactic and pyruvic acid blood levels (determined in blood taken one hour after oral ingestion of 1 8 gm of glucose per kg body weight) decreased markedly despite the fact that they continued to obtain the experimental diet that provided only 0 2 mg of thiamine per day At that time we were at a loss to explain the mechanism of the improvement but the present knowledge of tissue catabolism during bed rest offers an acceptable theory to resolve the problem Before the components of muscle tissue can be excreted by the kidneys they must appear in the blood stream This is true whether the bed rest follows partial nutritional deficiency or surgery or traumatic experiences such as fever fractures or burns One may not yet be prepared to state dogmatically that this catabolic process is based on the need for its valuable functional effects but it is reasonable to conclude that the vitamins and other nutrilites so presented to the circulatory system may be as useful as long as the severe catabolic process continues as any synthetic mixture of similar composition injected into the blood stream at that time The part of this stress phenomenon of importance to this discussion lies in the recognition that the organism in good nutritional state has the reserve to meet the requirements of this protective mechanism satisfactorily

What about the subject in poor nutritional state? Cuthbertson[7] has shown that rats in poor nutritional condition do not demonstrate this protein catabolic process and there is one report[8] of a patient in poor nutritional state with long standing rheumatoid arthritis who after multiple fractures failed to show any increase whatever in his protein catabolism Deciding whether the exhausted adrenocortical mechanism is primary or secondary to the depleted state of the nutritional reserves is too reminiscent of the chicken and-egg riddle so we shall omit further comment on this question

Observations of experimental riboflavin deficiencies in man have presented us with peculiar opportunities to evaluate a possible relationship between environmental trauma and the type of lesion obtained in ariboflavinosis Certain areas of the body such as the skin at the oral angles are subject to much wear and tear and subsequent danger of secondary infection Fissuring at the oral angles representing mild cases of angular stomatitis are not uncommon even in individuals in a good nutritive state During the first Elgin study on riboflavin deficiency a high percentage of such lesions were noted in both the

depleted and the riboflavin supplemented groups The lesions however were relatively mild and transitory in the 24 subjects who received riboflavin whereas 3 of the 15 subjects in the depleted group showed marked exacerbation of the oral lesions that could not be healed by topical therapy until after riboflavin was provided [7]

In a more recent study [8] a special attempt was made to evaluate the occurrence of these oral lesions In 6 out of 8 subjects on a diet that provided only 0 5 mg *of riboflavin per day there were 16 instances of angular stomatitis* Eight of these lesions with an average duration of about 4 weeks disappeared spontaneously before riboflavin supplementation The remaining 8 lesions were much more severe and required riboflavin supplementation to effect healing In 23 other subjects who were receiving 2 5 mg of riboflavin per day and were being observed simultaneously 7 fissures were seen in 4 subjects These were considerably less severe than those observed in the riboflavin depleted subjects and they lasted an average of three and one half weeks

To illustrate the course of these facial lesions and their possible relationship to infection the following example is given

A 30-year old white man developed a small herpes simplex lesion in the left

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buccal mucous membrane No therapy was applied Six weeks later a similar lesion appeared at the right oral angle without any preceding herpes infection Treatment with zinc oxide ointment and later with camphor liniment was then instituted The newer lesion the one on the right oral angle healed in about three weeks and did not recur The one on the left side continued in a fluctuating state of exacerbation and remission for several months Two months after the first appearance of the angular stomatitis the subject con

two months later a fissure formed at the left nasolabial lobe As the lesions had been present for about four months supplementation with 6 mg of riboflavin per day was instituted and the repair of the chronic facial lesions was quite definite and completed within one month Fresh herpetic vesicles appeared subsequently on two occasions but there was no recurrence of severe lesions while the patient received riboflavin

Some years ago Riddle Spies, and Hudson[9] showed that *Staphylococcus aureus* and *Streptococcus hemolyticus* could be isolated from lesions of angular stomatitis This is not surprising as the open wound presents an excellent medium for bacterial growth

In our experience the most characteristic sign of riboflavin deficiency in man has been the appearance of scrotal lesions and the only reasonable guess we can advance to explain this strange specificity is that this area is more subject to secondary infectious trauma Stannus,[10, 11] in 1912, was the first to record that

scrotal involvement may be the initial sign of deficiency in his pellagra patients Goldberger and Wheeler[19] reported that 6 out of 11 patients exhibited scrotal dermatitis before any other lesions of pellagra appeared and it should be noted that the diets of these patients provided less than 0 6 mg of riboflavin per day, which of course they did not know in 1920 With this knowledge as a background, it was relatively simple for the Elgin group to isolate, identify, and study this part of the total pellagra syndrome

An example of a relatively early phase of the scrotal dermatitis is given in FIGURE 1 Note the patchy redness associated with scaling and desquamation of the superficial epithelium The median commissure is uninvolved in most patients This stage was observed in 12 out of 15 subjects on the riboflavin depleted regimen of the first riboflavin project and in 5 out of 8 subjects in the second study Some of the subjects in the control groups exhibited signs of irritation and mild erythema, but in no case did any of these lesions approach the severity of the average in the depleted groups FIGURE 2 shows a later stage in another individual in which the scrotal lesion became quite raw and began to extend to the inner aspects of the thigh In another case not illustrated, some perineal inflammation was noted following which the scrotum became raw, oozing, and inflamed to such an extent that the lesion extended up the shaft of the penis

After the oral administration of from 2 to 6 mg of riboflavin per day the recovery from the severe lesions was dramatic Complete recovery was obtained in from one to five weeks FIGURE 3 is a photograph of the same scrotum shown in FIGURE 2 seven days after the diet of this patient was supplemented with 6 mg of riboflavin per day

The counterpart of the scrotal dermatitis in the male may be found in the vaginitis and vulval dermatitis that have been reported as part of the pellagra syndrome in females[13] but it has been difficult to document this supposition Since 1948 when experimentally produced scrotal dermatitis was first produced and repaired by riboflavin withdrawal and subsequent supplementation, respectively, we have tried to find some logical explanation for the phenomenon Why should more than half of all adult males who have subsisted for more than five months on diets containing less than 0 6 mg of riboflavin per day show such a specific lesion And this estimate includes Goldberger's subjects in whom the identical 'bilaterally symmetrical scaly lesions separated by a median band of normal skin" were clearly described Here is a lesion associated with a deficiency of riboflavin that added niacin does not prevent Why should this dermatitis appear in this special tissue and not in others? Our guesses have included consideration of local hygiene, perspiration, friction from clothes, or from the inner aspects of the thighs, the effects of residual detergents in clothes and of a variety of fungal infections, but none of our guesses, nor those of a corps of dermatologists, have been satisfying in the past All the factors mentioned, and more, may be contributory to the basic initial trauma

The scrotum differs from other tissues in that it has a large number of overlapping folds or rugae It is an elastic structure that expands and contracts with ordinary body movements and the work of the dartos muscle, and therefore has numerous points of epithelial contact Each point of contact within



F GURE 1 Early phase of sc otal de ma s obse ed af er 175 days on d et that pro d d 0 51 mg r bofla n pe day sub e t US)



F G RE 2 Mo e se e e l on of s otum obse ed n ano he pa ent ub e t AS) af e 299 days on d et that pro d d 0 55 mg bo la n pe day The e was no app e ab e hea ng of th s les on un l ofla n supp men tat on wa ro d 21 days la e



FIGURE 3 Demonstrates recovery of the same scrotum shown in FIGURE 2 seven days after subject AS was supplemented with 6 mg of riboflavin per day

the rugae may be an area where friction presents more local wear and tear than is ordinarily surmised Scrotal erythema like angular stomatitis is not necessarily a manifestation of ariboflavinosis If however as a consequence of local trauma, one obtains an infection or an insult to the tissue that must be repaired then the phenomenon of growth must come into play and a demand for riboflavin for new tissue is made When the subject is depleted he can no longer rob Peter to pay Paul *i e* bring in riboflavin from some other part of the body The erythema therefore becomes a dermatitis the dermatitis becomes a more severe lesion and so forth

Incidentally it may be proper to mention that there has been considerable confusion in our textbooks regarding what is or is not ariboflavinosis Indeed, the very existence of ariboflavinosis has been doubted The reason for this confusion is simple to explain It can be dogmatically stated that no investigator who has ever observed a group of adults on a daily intake of less than 0 6 mg of riboflavin for more than five months has failed to see the signs of ariboflavinosis which have been described by Sebrell and his co workers[14] Conversely those who have sought to produce this syndrome in adults in less time or have fed a daily level of intake of more than 0 8 mg per day for over a year have invariably failed to see any ariboflavinosis[15, 16] This does not imply that 0 8 mg per day is adequate or that much riboflavin could be stored for a future emergency on this intake but it does show that we may subsist for some time without obvious pathology at this level provided there are no major insults to the physical integrity of the individual in the meantime

If we extend our discussion of "reserve," or nutritional prophylaxis, to include consideration of aged individuals, we get into another nutritional dimension that is not too well understood. About a decade ago, it was the popular belief that the aged required more protein and vitamins than the young. This notion developed as a consequence of finding a higher incidence of nutritional disorders in old people. In order to check this notion an extensive collaborative study was inaugurated at the Elgin State Hospital by the Food and Nutrition board of the National Research Council.[6, 17] Among the general conclusions drawn from this research was the conviction that the similarities between the nutritional needs of the young and the old were greater than the differences, and that

not simplify the problem very much. For a variety of social and physiological reasons, the quest for food may become a less satisfying experience with advanced age and, with the decreased caloric intake associated with a general decrease in activity, the margins of safety for the intake of proteins and vitamins are violated. The loss of muscle mass usually noted in advanced age is by itself an indication of decreased nutritional reserve for defense against emergencies. You are all acquainted with the difficulties encountered in attempting to reverse the long term calcium losses of the aged. This long term calcium and nitrogen loss is very reminiscent of similar losses during short term bed rest, and one wonders whether the effects of decreased activity in advanced age is not physiologically related to the effects of decreased activity during bed rest. Whatever the explanation for this loss of stored nutrilites, it remains a fact that the

Let us remember that many compounds that the body cannot use must be metabolized or conjugated before they are excreted, and that added protein may cause additional unnecessary work for an already overtaxed circulatory system.

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on kwashiorkor[18] and on experimental protein deficiencies in man[19] have clarified somewhat *the earlier clinical observations of liver pathology produced* on deficient diets. While the possible relationship between liver function and resistance to infection cannot be stated simply, it cannot be denied.

At present, we are engaged in an attempt to determine whether adult men have a definite requirement for vitamin E. To date, after over a year of the experiment, we have found it difficult to deplete the reserves of vitamin E in the average adult and conclusions on the place of tocopherol in the course of human disease cannot yet be made. However, we have confirmed and elabo

rated in adult men[20] previous observations made in rats[21] and in infants[22] that the red blood cell is more susceptible to hemolysis by various agents when the tocopherol content of the plasma is decreased Whether or not this phenomenon will prove to be of physiological significance remains to be determined A recent report by Mason and Bergel[3] showed that *Mycobacterium leprae* can survive in vitamin E-deficient rats to produce lesions typical of human leprosy This work will be watched with much interest as the onset of leprosy has usually been associated with a poor nutritional state

In summary and conclusion we have tried to present a plea for more critical evaluation of animal experiments in which all or most of a given nutrilite is withdrawn from the diet and we have elaborated on the suggestion that some of the lesions noted in vitamin deficiency are a local manifestation of the retardation of growth The concept that the catabolic breakdown of tissue in stress may be a functional protective mechanism has been discussed from the view point of the need for adequate nutrilite reserves

While it is hoped that every cracked lip furrowed tongue sore gingiva or conjunctivitis will not be diagnosed as a nutritional deficiency it is also hoped that justifiable criticism of poor interpretations will not blind us from recogniz

spectacle that we hope will immunize our children against a relatively rare disease As I approach middle age and lose some of the skepticism of youth—and I must confess to having been a strong opponent of vitamin overfeeding—I cannot help but wonder in retrospect whether vitamin prophylaxis or the feeding of more than the minimum requirements if you will has not been at least as useful to the nation s health as the more obvious forms of immunological prophylaxis

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NUTRITION AND INTESTINAL PARASITISM

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The animal parasites that inhabit the intestinal tract of man and other animals present unique problems in relation to host parasite relationships These animal parasites represent a wide variety of forms from the single celled protozoan parasites to the highly complex metazoa with in many instances complicated life cycles No species of animal is susceptible to all parasites and no parasite is able to infect all hosts This discussion will be limited primarily to those parasites who as adults are primarily limited to the intestinal tract of the host In some instances the animal parasite in the adult stage remains in the lumen of the intestinal tract with no attachments to the tissue In others there will be direct invasion of the wall of the intestine The extent of tissue invasion will vary from a direct attachment as in hookworm disease to invasion of the wall of the intestine as in amebiasis and strongyloidiasis or as in ascariasis with the adult living in the lumen of the intestine with no direct attachment or invasion of tissue by the adult worm

There are many factors that may contribute to the relationships between the host and the parasite The food of the host is of extreme importance and is closely linked with the physiologic state of the host In the intestinal tract, with changes in nutrition there may be a direct effect on the environment of the parasite and thus a possible alteration of the relationship between the host and the parasite In general parasites that can establish themselves with the least damage to the host have the best chance for prolonged residence in that host since in such cases the host response to the presence of the parasite is meager or generally ineffectual The best adjustment of parasite and host is usually found in parasites limited to the alimentary canal Humans may harbor in their intestinal tract tapeworms such as *Taenia saginata* or flukes such as *Fasciolopsis buski* for many years with no physical effects so long as the diet is sufficient for both the individual and his parasite Likewise the intestinal flagellates as a group as well as the nonpathogenic amebae may persist in the intestine for years without the host being aware of the infection since these forms are normally harmless commensals In animal parasitism the extent of damage produced to the host tissue will vary greatly and there are many complex factors which must be considered in attempting to explain the pathogenesis of the various forms

The capacity of a host to resist the destructive action of a given parasite is sometimes due to the natural resistance of that host In some instances this gives complete protection of the host from the parasite Such natural resistance is not always present at birth but sometimes it is developed against certain parasites only after the host has neared maturity In contrast to this type of resistance the host in some instances remains susceptible to infection with certain animal parasites during an entire lifetime In such instances there develops in such a susceptible host on first exposure to a specific parasite an

creased. The results of this extensive series of experiments furnished further evidence that specific vitamins are important factors in host resistance to helminthic infections.

These experiments, while not permitting a blanket statement that deficient host diets react to the benefit of the parasite, do indicate that resistance is lowered to helminthic infections, both in the somatic and intestinal phases, when omnivorous hosts are maintained on diets deficient in A, B complex, or D, or on rations with highly restricted sources of protein. These various studies have also shown that the degree of natural and acquired resistance of a host to its helminth parasites is dependent to a large extent upon its diet, its genetic constitution, and its age. Diets of man and other omnivorous animals, to serve in developing the most potent resistance to helminth infections, must include adequate specific vitamins, minerals, and other substances essential to a well balanced ration.

In contrast to the helminths found in the intestinal tract, the single celled protozoan parasites present a somewhat different problem. A large number of protozoan parasites live in the lumen of the intestinal tract of man and other animals and depend essentially on the diet of the host for their food. Nutritional factors do play an important part, however, in the host parasite relationships in that certain dietary changes may contribute to the decrease of resistance on the part of the host, thus contributing to the production of damage by the parasite.

Protozoologists have long recognized the effect of diet of the host upon the parasite. Hegner[14] in 1924 suggested that a "carnivorous diet," one high in animal protein content, was unfavorable for certain intestinal protozoa of mammals. Hegner and Eskridge[15] showed that rats infected with the human flagellate, *Trichomonas hominis*, when fed a diet rich in animal protein, produced an unfavorable condition in the cecum of rats for growth and development of this flagellate. Hegner and Eskridge[16] also demonstrated that the conditions in the cecum of rats were rendered more favorable for trichomonads when a liver diet was substituted for the normal diet which consisted largely of carbohydrates. Frye and Meleney[17] found that lack of vitamin A in the diet was not the cause of the inability to establish or maintain infection with *Endamoeba muris* in the rat. Neither the lack of vitamin A in the diet nor the condition of A deficiency in the rats rendered the lumen of the cecum unsuitable for the development of *E. muris*. Ratcliffe[18] showed experimentally that a high protein diet favoring proteolytic bacteria in the intestinal tract decreased the intensity of natural infections with *Endamoeba muris* in mice.

Kagy and Faust,[19] Faust and Kagy,[20] and Faust, Scott, and Swartzwelder[21] demonstrated that, in dogs, fulminating experimental amebic colitis could be controlled with raw liver, which at times even produced cure. Faust and Swartzwelder[22] demonstrated that liver extract, introduced parenterally, had no effect on the progress of the lesions or symptoms. This is in marked con

prevents erythropoiesis, or that its amebastatic action is inhibited when it is

introduced intramuscularly Faust, Scott, and Swartzwelder[21] noted that dogs resistant to infection on a normal diet could usually be infected if they were placed on canned salmon Kittens fed on salmon diet are also more susceptible to infection with *F histolytica*

In the literature on amebiasis, McCarrison [23] and Kagy and Faust[19] refer to diet as a factor in the development of the clinical manifestations of this disease It was noted by Frye and Meleney [24] in studies of the pathogenecity of a number of strains of *Endamoeba histolytica* that monkeys fed on a normal diet did not develop lesions with certain strains of *E histolytica*, although numerous amebae were found in the lumen and deep in the glandular crypts but with no evidence of tissue pathology or invasion One monkey in this study became emaciated and extremely ill At autopsy this animal was found to have tu

resistance and the production of tissue pathology by the parasite McCarrison[25] showed that monkeys that were chronic carriers of *E histolytica* developed

certain instances they became completely parasite free Larsh[27] showed that in dogs kept on a black tongue deficient diet the virulence of the infection with *E histolytica* is enhanced and that the lowered resistance of these animals was related to a deficiency of nicotinic acid Taylor and his co-workers[28] demonstrated that guinea pigs became highly susceptible to *E histolytica* infection when fed rat ration pellets and that they are even more susceptible when fed a

set up a controlled study of the effect of ascorbic acid deficiency in guinea pigs experimentally infected intracecally with *Endamoeba histolytica* trophozoites

effect on those fed a mildly scorbutogenic diet of natural foodstuffs was intermediate between the two groups The ascorbic acid deficiency in these experiments seemed to render the disease much more fulminating in the guinea pig Numerous experimental and clinical observations have demonstrated the importance of ascorbic acid in the phenomenon of resistance to infection Perla and Marmorston[?] showed that the influence of this vitamin on resistance is dependent at least in part on its role in the production of intercellular sul

Several investigators have suggested that diet influences the incidence course

and final outcome of amebic infection in man Alexander and Meleney[33] reported the results of a dietary study in two rural communities in Tennessee in which studies of amebiasis had previously been made In one community acute amebic dysentery was common, in the other, it was very rare although 40 per cent of the people in the community harbored *Endamoeba histolytica* In the community with little or no acute amebic dysentery, the diet was more adequate in calories and vitamins than in the area where acute amebic dysentery was common In the community where the amebae showed less pathogenic activity milk, green vegetables, and fruit were more prominent in the diet It was also found that the distribution of protein, fat and carbohydrates in the diets was about the same in the two communities This study indicated that where the diet was more adequate, evidence of acute infection with *E histolytica* was rare

Elsdon Dew[34] observed that in Durban, South Africa, where indigenous Bantus, Indians, and Europeans live side by side, amebiasis affects these three races in different ways Among the maize eating Bantus, acute fulminating dysentery is common Among the Indians who traditionally eat curry and rice, acute amebic dysentery is rare but liver abscess is often encountered Among the Europeans who have a full essentially balanced diet, severe amebiasis seldom occurs As a result of his long experience Doctor Elsdon Dew suggests that dietetic deficiencies are responsible for these differences In comparing the incidence of amebiasis among the Africans in Durban and in Lorenco Marques (Mozambique) Elsdon Dew[34] attributed the strikingly lower rates of amebic dysentery in the latter to a supplement of fish, rice, and many vegetables Sautet and his co workers[35] believe that food shortages and consequent deficiencies in essential elements of nutrition have been responsible for the increased incidence of amebiasis and other intestinal parasitic diseases in Marseilles during and immediately after the end of the war

gators Attempts have been made to determine why this parasite produces

also demonstrated that interchange of bacterial associates between strains did

[illegible] pathogen[illegible] The question of strain differences

toms in those patients harboring only small race but that apparently healthy

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to severity of infections with *E histolytica* The classical experiments of Walker and Sellards[10] intimated that natural resistance was responsible for the failure of some human volunteers to exhibit dysentery with strains of amebae that caused disease in other individuals Acquired immunity has been considered by some to account for the decline of amebiasis as is seen in humans beyond middle life Neither is there a clearly demonstrable lasting acquired immunity in man following infection and very little evidence in animals The best of such immunity evidence in animals is seen in the work of Swartzwelder and Avant[11] who found that dogs following spontaneous recovery or after removal of *E histolytica* by therapy were markedly resistant to reinfection The evidence now available indicates that in order for *Endamoeba histolytica* to produce gross tissue pathology in the intestinal tract there must be a minimal of host resistance together with the accessory action of the intestinal bacteria dietary deficiency and other factors The ability to control tissue pathology by alteration of one or all of these factors in man has never been demonstrated The local condition of the host tissue certainly influences tissue invasion Dietary deficiency as has been demonstrated in

[illegible]

[illegible] lowed 66 patients with no specific therapy These patients were placed on dietary supplements and bed rest but no other therapy of any kind In this group of 66 patients 39 were assigned to a specific treatment schedule before the end of the six weeks follow up period 11 of the 66 patients had no clinical or parasitological evidence of amebic infection These 11 patients by the standards used in the study would be counted as successfully treated In addition five other patients with stools still positive for *E histolytica* had recovered clinically This group of acute amebic dysentery patients studied and followed along with specifically treated cases is the only such example found in the literature on amebiasis What part the dietary supplements played in spontaneous recovery cannot be determined from this study It seems quite possible that the deficient diet

[illegible]

was a definite reduction in number of acute cases, although the prevalence of *E histolytica* was still very high

In an epidemic of amebiasis studied by Sappenfield *et al*[43] and traced to a possible contamination of a plant water supply, the number of clinically recognized cases were in marked contrast to the Korean prisoner group The beginning of this outbreak was obscure but probably occurred several years before it was recognized A concentration of recognized clinical amebiasis developed in the late winter of 1953 There were a few cases of amebic abscess of the liver The total number of recognized cases of acute amebiasis was small in comparison to the Korean prisoners A careful epidemiological study and a stool survey of this group revealed that over 50 per cent of the employees harbored *E histolytica* but at the time the stool survey was made, there was no clinical evidence of disease in any of these individuals Here we have a group of humans infected with *E histolytica* having a well balanced diet, good housing and other living conditions, in marked contrast to the Korean group

following the administration of Terramycin and Tetracyn, given with vitamin supplements and milk, there are practically no side reactions A group of 75 children between the ages of 3 and 10 years has been treated for amebiasis with Tetracyn Tetracyn, dispensed as pediatric drops, was used in this series with a daily dose of 25 mg per kilogram given over a period of six days There were no side reactions to the therapy, and some patients actually had *an increase in appetite and slight weight gain Stool examinations one* week and one month after completion of therapy showed excellent results, but the final evaluation of therapy will be deferred until after a three months' follow up period

Discussion It has been clearly demonstrated by controlled laboratory experiments that nutrition is an important factor in the defense mechanisms of the host against certain intestinal parasites It seems evident that the conditions necessary for invasion or infection of the intestinal tract differ only slightly from those necessary for infection of the skin or other host tissue Improper or inadequate food supply may produce changes in the tissue unfavorable to the host and at the same time favorable to the parasite The adjustments between the parasite and host are often extremely delicate, and only slight changes may mean the difference between no evident pathology and marked damage to the host tissue and gross pathology produced by the parasite

The experiments showing the relation of dietary factors in various helminth infections is striking Specific vitamin deficiencies have been shown to favor the parasite and at the same time to produce definite interference with host resistance It has also been established by laboratory experiments that diet is a factor of singular importance in altering the ability of the host to combat certain intestinal helminth infections

Investigators interested in the intestinal protozoa of man and of other

animals have long recognized the effect of diet of the host upon these parasites Well-controlled experiments have demonstrated the importance of dietary factors on the pathology of amebiasis Higher infectivity and mortality rates and a more severe type of amebiasis have been demonstrated in animals fed a purified diet deficient in specific vitamins There is little doubt that dietary factors, under certain conditions, play an important part in the pathology of amebiasis in man In certain parts of the world, evidence indicates that dietetic differences account for variations in the severity of infection with *E. histolytica* A careful epidemiological study of two epidemics of amebiasis offer interesting possibilities as regards the importance of nutritional factors in relation to resistance of the host

and Blumenthal *et al*[44] suggested that repeated bacterial infections with accompanying trauma to the intestinal mucosa may be an important factor in the occurrence of amebic dysentery During the seven month period of investigation of diarrhea and dysentery in the prisoner of war camp in Korea, there were approximately 2000 cases of acute shigellosis and many other undiagnosed gastrointestinal infections These infections may have been a contributing factor in predisposing the intestinal mucosa to invasion by *E. histolytica* It was evident, however that with a more adequate diet, combined with better sanitation, all the gastrointestinal infections decreased in number and in severity

Host resistance to invasion of the intestinal tract by certain animal parasites can be altered markedly by dietary changes The importance of the various nutritional factors in the repair of damaged tissue and the treatment of these infections has been demonstrated

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Discussion of the Paper

Doctor A H Mousa (*Kasr El Aini Faculty of Medicine Cairo, Egypt*) I should like to add a few words to what Professor Frye has said about amebiasis

The relation of malnutrition to intestinal invasiveness of *Endamoeba histolytica* as well as to its extraintestinal hepatic localization was not found clinically high by Mofty and myself in a study of a group of malnourished peasants compared to a similar group of well nourished city dwellers Faust recorded the same observation in the West Indies, and he explained it by the difficulty of encystment of amebae in patients living mainly on a carbohydrate diet maize which produces an acid stool Professor Mogrocki, in a personal communication demonstrated experimentally the importance of allergy in the development of liver abscess in animals Allergy is manifested in well nourished cases to a greater extent than in malnourished ones

An important factor in the observation of other workers who have shown a higher incidence of amebic dysentery in malnourished cases is based on the higher incidence of bacterial dysentery in cyst passers This must be differentiated from cases of acute amebic dysentery or chronic amebic dysentery with acute exacerbation in both of which vegetative forms must be demonstrated

THE EFFECT OF HIGH LEVELS OF VITAMINS ON THE RESISTANCE OF CHICKS TO FOWL TYPHOID

By C H Hill and H W Garren*
North Carolina State College Raleigh N C

Studies throughout past years have established clearly that the development of resistance to disease is subject to both genetic and environmental influences It is fair to say that diet is the environmental influence that has been studied most extensively Since the discovery of vitamins and the recognition of their essential role in the maintenance of normal cellular metabolism these substances are probably the most studied of the various constituents of the diet Indeed it is recalled that it was a study of the then supposedly infectious disease of beriberi by Eijkman that led to our modern concept of vitamins

The studies on the relationship of nutrition to disease have been reviewed in recent years by Schneider[1] and Clark *et al*[2] The investigations on the role of vitamins in resistance to disease have been concerned in general with deficiencies of an individual vitamin or group of vitamins The correlation between a vitamin deficiency and resistance to disease has been found to be positive in some cases and negative in others

For example Wooley and Sebrell[3] have shown that riboflavin or thiamine deficiencies decrease resistance of mice to pneumococcal infection On the other hand Reiner and Paton[4] found that rats on a vitamin B complex deficient diet were more resistant to *Trypanosoma equiperdum*, as indicated by a prolongation of the incubation time over that of controls fed a diet containing a vitamin B complex supplement

While the results of studies on the effect of vitamin deficiencies in response to disease are of fundamental importance, they are difficult to interpret in terms of resistance of the host animal There is little in our knowledge of

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are not plentiful even less data are available on the effect of high levels of vitamins In the studies of Wooley and Sebrell[3] mentioned above, the administration of 5 to 10 times the amount of riboflavin or thiamine given the control groups did not increase the resistance of mice to pneumococcal infection There are a few other instances in which an exceedingly high level of an individual vitamin has been tested No one to the authors knowledge however has tested the effect of the inclusion at high levels of all the known required vitamins on resistance to disease This is the approach that has been taken in the experiments presented in this report

In all the studies presented herein rapidly growing strains of New Hamp-

* The authors are deeply indebted to Merck and Company Inc Rahway N J for most of the vitamins used throughout these studies and to the Lederle Laboratories Pearl River N Y for supplies of folic acid

shire or White Rock chicks obtained from a commercial hatchery were used. Forty birds were used per treatment in each experiment. The chicks were weighed, wingbanded and placed on experiment the day they hatched. The experimental period was divided into two parts: a preinoculation period of four weeks and a postinoculation period of approximately three weeks. In order to minimize any effect that differences in total feed intake might have on resistance to disease, the feed intake of all lots was equalized during the preinoculation period. During the postinoculation period, feed was supplied *ad libitum*. Water was supplied *ad libitum* throughout the experimental period.

At four weeks of age the birds were inoculated with a culture of *Salmonella gallinarum*, the fowl typhoid organism. The organism was grown overnight on proteose No. 3 agar (Difco) at 37°C. The bacteria were washed from the agar with sterile saline (0.85 per cent) and diluted with sterile saline to a reading of 8 to 12 per cent light transmission on a Coleman spectrophotometer model 14 using a PC-4 filter at wave length 650 μ. One ml. of this suspension was given orally to each chick.

The resulting disease was allowed to run its natural course, and the experiments were terminated when the chickens had ceased to die and appeared to be recovering rapidly from the effects of the infection. This was usually approximately three weeks from the date of inoculation.

The experimental diets were fed from the day of hatching. The basal diet used throughout these experiments is presented in TABLE 1. This diet is a simplified diet containing no animal protein. It meets the requirements for vitamins, amino acids and minerals that have been established by the National Research Council, Washington, D. C. for chicks in the disease free state. The vitamin content of the diet as well as that of the mixture is presented in TABLE 2. For comparative purposes, the vitamin requirements of the chicken are included in this table. It will be noted that with one exception all vitamins are present in excess of the requirements. While the vitamin B_{12} content appears not to meet the requirement, it has not been possible to show difference in requirements between the 3 μ and 4 μ per pound level when chicks were hatched from eggs laid by hens fed commercial diets.

When multiples of vitamin levels are referred to throughout these studies, the reference is to multiples of the vitamin supplement. The vitamin supplement was mixed with ground yellow corn so that when the vitamin levels were increased, the corn in the basal diet was decreased, thus keeping the diets identical except for the vitamin level.

The purpose of the first experiment was merely to determine if high levels of the required vitamins had any effect on the resistance of chicks to fowl typhoid. In this experiment ascorbic acid was included in the vitamin supplement. This was done for two reasons. First, although the chicken supposedly does not require a dietary source of ascorbic acid, there have been reports[6, 7] that in some instances beneficial effects have been obtained when this vitamin is included in the diet. Second, in animals that do require a dietary source of ascorbic acid some evidence exists[8, 9] that it may be concerned in disease resistance. The other vitamins were included at a level 10 times that of the basal supplement. The results of this study are presented in TABLE 3.

TABLE 1
BASAL DIET

	Per cent
Soybean meal	47.0
Yellow corn	48.0
Phosphate	2.0
Limestone	1.5
Salt	0.5
Methionine	0.3
Vitamin mix	0.5
Choline chloride	700 mg/lb
$MnSO_4$	100 mg/lb

TABLE 2
VITAMIN CONTENT OF THE BASAL DIET

Vitamin	Supplement/lb	Total	Required
Thiamine (mg)	0.9	2.1	1.3
Riboflavin (mg)	1.6	2.5	1.3
Niacin (mg)	8.0	17.0	12.0
Pantothenic acid (mg)	5.0	8.4	4.2
Folic acid (mg)	0.45	1.55	0.25
Biotin (mcg)	45	81	40
Pyridoxine (mg)	1.6	8.7	1.3
Choline (mg)	700	1460	600
Vitamin B_{12} (mcg)	3	3	4
Vitamin A (I.U.)	3000	4100	1200
Vitamin D(I.U.)	180	180	90
Menadione (mg)	10	10	0.20
Vitamin E (mg)	10	10	—

TABLE 3
INFLUENCE OF EXCESS VITAMINS ON RESISTANCE OF CHICKS TO FOWL TYPHOID

Diet	Avg. days survival time	Per cent total survival
Basal	8.5	10
10 × vitamins + C, 0.1%	12.8	40

Note Survival time calculated from day of inoculation till day of last death in experiment

The inclusion of the high levels of vitamins increased the percentage of surviving animals from 10 to 40 and increased the average survival time. Thus it was tentatively assumed, pending confirmation, that high levels of vitamins did enhance resistance to fowl typhoid.

It was important to determine whether or not the enhanced resistance due to high vitamin levels was due to a single vitamin or group of vitamins, or whether the entire combination of vitamins was necessary for this effect. Studies were undertaken, therefore, to determine the effect of groups of vitamins on resistance to fowl typhoid. For the purposes of this study, the vitamins were arbitrarily divided into the fat soluble group, the water soluble B vitamin group, and ascorbic acid. Each vitamin in the various groups was

TABLE 4

INFLUENCE OF EXCESS VITAMINS ON RESISTANCE OF CHICKS TO FOWL TYPHOID

Diet	Avg days survival time	Per cent total survival
Basal	12 2	48
10 × vitamins + C 0 1%	15 0	76
0 1% vitamin C	11 0	34
ADEK	8 6	15
Water soluble vitamins	11 0	25

Note Survival time calculated from day of inoculation till day of last death in experiment Experimental period [illegible] day

fed at the same high level as it was fed in the complete high vitamin supplement The results of this study are presented in TABLE 4

Again, the feeding of high levels of all the required vitamins resulted in an increase in total survival and average survival time The various groups tested however, showed no beneficial effect In fact the high levels of fat soluble vitamins, A D, E and K considerably decreased both total survival and average survival time The importance of this finding awaits confirmation and further work

The results of this study clearly show that the effect of high levels of vitamins on resistance to fowl typhoid is not due to a single vitamin but to some combination of vitamins distributed between the groups tested Studies were directed therefore toward determining which vitamins were necessary in this combination These studies were carried out using the high vitamin supplement of all vitamins except the one under test This vitamin was present at the same level as in the basal group Thus if the absence of a vitamin from the vitamin supplement did not lower the resistance from that obtained with the complete vitamin supplement, that particular vitamin was considered to be not essential for increased resistance to fowl typhoid under the conditions employed The results of these studies are presented in TABLE 5

It was observed that, of the first group of vitamins tested only choline could be omitted from the high vitamin supplement without lowering the resistance over that obtained from the complete vitamin supplement The fat soluble vitamins vitamin B_{12} pyridoxine and ascorbic acid were all required in the vitamin mixture

The results of the experiment on the second group of vitamins tested are more difficult to evaluate due to the fact that, eventually mortality reached essentially the same level in all lots The prolongation of the average survival time, however indicates that the complete vitamin supplement promoted greater resistance early in the postinoculation period The absence of riboflavin or niacin from the complete vitamin supplement lowered this early resistance The absence of thiamine biotin, folic acid or pantothenic acid, however apparently increased the resistance of the chicks

These results show that the absence of an individual vitamin from the complete high level of vitamin supplement can express itself in three ways in relation to the resistance obtained with the complete high level supplement The absence can lower the resistance it can apparently increase the resistance, or

TABLE 5

EFFECT OF INDIVIDUAL VITAMINS ON THE RESISTANCE OF CHICKS TO FOWL TYPHOID

Diet	Days avg survival time	Per cent survivors
Experiment I		
Basal	12.9	61
10 × vitamins + 0.1% C	15.1	83
10 × vitamins − C	12.2	50
10 × vitamins − K	12.2	54
10 × vitamins − E	12.8	62
10 × vitamins − D	12.7	63
10 × vitamins − A	10.1	39
10 × vitamins − B_{12}	12.4	58
10 × vitamins − B_6	11.8	54
10 × vitamins − choline	15.0	90
Experiment II		
Basal	8.2	19
10 × vitamins + 0.1% C	8.8	16
10 × vitamins − riboflavin	7.4	8
10 × vitamins − niacin	7.6	8
10 × vitamins − thiamine	9.5	21
10 × vitamins − biotin	10.3	20
10 × vitamins − folic acid	10.0	29
10 × vitamins − pantothenic acid	9.7	25

TABLE 6

EFFECT OF OMISSION OF INDIVIDUAL VITAMINS FROM A HIGH LEVEL VITAMIN SUPPLEMENT ON RESISTANCE TO FOWL TYPHOID

Lowers resistance		*Increases resistance*	
Vitamin A	(3.4)	Thiamine	(1.6)
Vitamin D	(2.0)	Biotin	(2.0)
Vitamin E	(—)	Folic acid	(6.2)
Vitamin K	(50)	Pantothenic acid	(2.0)
Vitamin B_{12}	(0.75)		
Pyridoxine	(6.7)		
Riboflavin	(1.9)	*No effect*	
Niacin	(1.4)	Choline	(2.4)
Ascorbic acid	(—)		

Note Figures in parentheses indicate multiples of requirements present in the basal diet

it can have no effect on the resistance The results obtained are summarized in this manner in TABLE 6

The figures in parentheses in this table indicate the level of the vitamin in the diet in relation to its requirement This is the level that resulted when the vitamin was omitted from the high level vitamin supplement It also represents, therefore, the level in the basal diet in relation to requirement

The data obtained considered in this manner, present several interesting aspects It is apparent that the increased requirement for vitamins for increased resistance is not merely a certain multiple of each vitamin requirement Vitamin K at 50 times the requirement, is not sufficient for maximum resistance, while 2.4 times the requirement for choline is sufficient, and 2 times the

biotin requirement apparently results in greater resistance than does 20 times the requirement

Another important aspect of these results is the finding that ascorbic acid was important in promoting resistance to typhoid when used with high levels of other vitamins although alone it had no effect on resistance Since the chicken supposedly has no dietary requirement for ascorbic acid, this finding required further investigation

It is well known that ascorbic acid inhibits the growth of certain organisms Thus the effect of ascorbic acid might have been due to its antibacterial effect against the *Salmonella* organism in the intestinal tract of the chicks Another possibility was that the effect of ascorbic acid was due to its antioxidant properties and thus this effect might not be specific for ascorbic acid Experiments were therefore designed to determine more precisely the role of ascorbic acid in protecting the chicks against fowl typhoid

In these studies ascorbic acid was fed at the 0 1 per cent level in combination with high levels of the rest of the vitamins as in the previous experiments In addition a lot was fed a high level of all the vitamins except ascorbic acid This lot was injected with ascorbic acid starting at the third week in the preinoculation period and continuing until the end of the experimental period The ascorbic acid was injected intramuscularly daily in the same amounts as were consumed by the birds receiving the ascorbic acid in their diet Another lot was fed diphenyl phenylenediamine (DPPD) another antioxidant which is being used for various purposes in poultry feeds The results of these studies are presented in Table 7

Again the high level of vitamins with 0 1 per cent ascorbic acid increased the resistance of the chicks as measured by a prolongation of the average survival time The ascorbic acid injected was even more effective than the orally administered ascorbic acid increasing the percentage of survival from 19 to 46 Furthermore the other antioxidant used DPPD was even more effective than ascorbic acid in the diet DPPD alone like ascorbic acid alone was ineffective in increasing resistance to fowl typhoid

From these results it is apparent that the effects of ascorbic acid are most probably due to some action in the body and not in the intestinal tract This effect is apparently due to the antioxidant properties of ascorbic acid since it can be replaced by another antioxidant in the diet of the animal

Table 7

Effect of Ascorbic Acid and DPPD on Resistance of Chicks to Fowl Typhoid

Diet	Days average survival time	Per cent survivors
Basal	8 2	19
10 × vitamins + 0 1% C	8 8	16
10 × vitamins + injected C	11 5	46
10 × vitamins + DPPD	10 6	30
Basal	8 2	20
10 × vitamins + 0 1% C	8 8	35
DPPD	[illegible]	1

TABLE 8
EFFECT OF INCREASING LEVELS OF VITAMINS ON RESISTANCE OF CHICKS TO FOWL TYPHOID

Diet	Days avg surv val t me	Per cent surv ors
Basal	8 2	19
2 5 × vitamins + 0 1% C	8 2	3
5 0 × vitamins + 0 1% C	10 0	30
7 5 × vitamins + 0 1% C	9 2	23
10 0 × vitamins + 0 1% C	8 8	16

Another interesting aspect of the data presented in TABLE 6 is the observation that the omission of thiamine, biotin, folic acid, and pantothenic acid from the high level vitamin supplement apparently increased the resistance of the chicks A possible explanation of this finding is that the high level of vitamin supplement used throughout these studies may have been too high to obtain maximum resistance to fowl typhoid In order to test this possibility, a series of vitamin levels were fed containing 2 5, 5 0, 7 5, and 10 0 times the level of the vitamin supplement contained in the basal diet The results of this study are presented in TABLE 8

The level of vitamin supplement 2 5 times that of the basal diet had no effect on mortality or average survival time The addition of five times the

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difficult to interpret in terms of resistance of the host It is presumably possi

vitamin level of the diet has two effects in the disease system one on the host resulting in increased resistance to typhoid, and the other on the *Salmonella* organism, increasing its disease producing capacity Thus, five times the basal vitamin supplement level may produce the maximum resistance in the host that this particular dietary manipulation is capable of producing It might still be possible however, to increase the disease producing capacity of the organism by further increases in vitamin levels These further increases would result, then in a more acute expression of the disease not because of decreased resistance of the host, but because of the increased disease producing capacity of the infectious agent

In order to evaluate this hypothesis, an experiment was conducted in which

this experiment are presented in TABLE 9

In this experiment the level of the vitamin supplement 7 5 times that given the basal group resulted in the greatest percentage of survivors when the organism was given orally When the level of the vitamin supplement was increased to 10 times that of the basal group, the percentage of survival was

TABLE 9

EFFECT OF INCREASING LEVELS OF VITAMINS ON RESISTANCE OF CHICKS TO FOWL TYPHOID

Diet	Days avg survival time		Per cent survivors	
	Oral	Injected	Oral	Injected
Basal	10 8	6 0	17 9	5 3
5 0 × vitamins + 0 1% C	11 6	7 2	27 5	10 0
7 5 × vitamins + 0 1% C	14 0	6 5	52 5	5 3
10 0 × vitamins + 0 1% C	12 2	8 4	37 5	22 5

reduced over the 7 5 times level When the organism was inoculated intramuscularly however the highest level of vitamin supplement resulted in the greatest number of survivors Since no plateau of response was reached in the groups inoculated intramuscularly, no conclusion can be drawn in regard to the hypothesis tested These results, however, confirm the previous finding that it is possible to supplement the diet to a level of vitamins too high to produce maximum resistance to fowl typhoid Furthermore, the effect of high levels of vitamins in increasing the resistance to this disease is apparent even when the organism is introduced intramuscularly Further studies will have to be conducted with still higher levels of vitamins to determine whether a plateau in response to vitamins can be reached when the organism is inoculated intramuscularly If such a plateau is reached, and if further increases in vitamin levels of the diet do not result in lowering of the survival rate this may be presumed to be evidence that the apparent decrease in resistance occurring when the highest vitamin levels are fed to groups inoculated orally is due to the effect of the highest levels of vitamins on the infectious agent and not on the host

In summary the results of the studies presented in this report clearly demonstrate that high levels of all the known required vitamins increase the resistance of chicks to fowl typhoid The enhanced resistance observed when high levels of vitamins are fed is apparently not due to a uniform increase in requirement for all vitamins Some vitamins, such as vitamin K must be increased over the requirement for growth many times more than others such as choline, in order to bring about increased resistance to typhoid In addition to the essential vitamins at high levels an antioxidant is required in the diet in order to increase the resistance of the chick to fowl typhoid

This antioxidant apparently exerts its influence in the body of the chick Either ascorbic acid or diphenylphenylene diamine can act as the required antioxidant Lastly it is possible to oversupplement the diet with vitamins in so far as obtaining maximum resistance to oral inoculations of the *Salmonella* organism The exact mechanisms of all the phenomena observed in these studies are not known and they await further study

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ANTIBIOTICS AND VITAMINS IN THE TREATMENT OF SWINE ENTERITIS*

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It is the consensus of pathologists specializing in swine that there are probably several forms of enteritis in swine Among these investigators, Doyle (1943) has shown that an acute hemorrhagic dysentery is a disease distinct from necrotic enteritis In addition to swine dysentery, the importance of cholera in swine enteritis was shown by Gibbs (1933) This investigator isolated the virus of hog cholera from the intestines of runt pigs showing enteritis (button like ulcers) as long as 94 days after an outbreak of hog cholera In this connection, Doyle and Walkey (1946) proved experimentally that the feeding of viscera from pigs affected with what was 'commonly diagnosed as necrotic enteritis" to cholera vaccinated pigs produced no clinical symptoms of disease When parts of the same viscera were fed to cholera susceptible pigs, however, one half of them showed lesions of hog cholera and enteritis The remaining pigs were unthrifty for some time This would indicate that the virus of hog cholera produced a form of enteritis

The remaining forms of enteritis consist of a complex group of conditions characterized by necrosis of the intestinal mucosa, and sometimes of the submucosa While there were those who considered enteritis as a filth-borne disease attributed to an invasion by the organism *Salmonella choleraesuis*, a few investigators recognized the possibility that nutritional factors might be involved

Under practical feeding conditions in the United States, the diet of the pig is made up largely of corn, a condition that has prevailed for a great many years Hart and McCollum (1914) were among the first to study the nutritional requirements of swine with special emphasis on corn It was early recognized by these investigators that pigs could not be raised on corn alone but that if such a diet were supplemented with minerals and feedstuffs high in protein, good growth could be obtained A few other studies were reported, but no particular studies were designed to study the needs of swine for vitamins of the B group until work was undertaken by Chick and his associates of England and Hughes of California

Previously, however, Miller and Rhoads (1935) had chosen pigs as experimental animals for the attempted reproduction of a condition similar to pernicious anemia since tests on dogs had failed to prove satisfactory As far as this writer is aware these workers were the first to feed a modified Goldberger Wheeler diet to pigs They reported that diarrhea was a frequent finding, along with loss of appetite stomatitis, achlorhydria, and anemia It certainly should be considered extremely interesting that they produced a syndrome in pigs that the authors considered to resemble in many respects, pellagra in man and blacktongue in dogs

* Published with the approval of the Director of the Michigan Agricultural Experiment Station East Lansing Mich as Journal Article No [illegible]

Niacin deficiency At about this time, studies were showing that the rat was apparently not a suitable animal for the investigation of the pellagra preventive and blacktongue preventive factors which appeared to be identical The English workers (Birch *et al*, 1937) turned to the pig Modified Goldberger Wheeler diets were used and in general, these investigators found that one or more substances were lacking and that the deficiency was in the B-complex rather t
of appetite
of the muco
with a fibrinous adherent membrane In a subsequent paper, Chick *et al* (1938) reported that nicotinic acid both prevented and cured the deficiency symptoms

This writer s interest in the nutritional aspects of swine enteritis was stimulated by previous work carried out at the Michigan Experiment Station by Davis and his associates (Davis *et al* 1940) This work indicated that niacin deficiency in pigs was perhaps more prevalent under farm conditions than had hitherto been recognized Furthermore the work of the Wisconsin group (Krehl *et al* 1945 1946) *in establishing the relationship between niacin* and tryptophan in the rat explained why pigs fed high corn low protein diets developed severe niacin deficiency even though the same ration contained seemingly adequate amounts of the vitamin

The work of Luecke *et al*, 1947 and of Luecke *et al*, 1948, established for the pig the role played by tryptophan in niacin deficiency This work indicated that the niacin requirement of the pig could be at least doubled when fed high corn diets low in tryptophan

Pantothenic acid deficiency Another vitamin of significance in practical swine nutrition is pantothenic acid

With the advent of synthetic calcium pantothenate both Hughes (1942) and Wintrobe *et al* (1942) demonstrated that the feeding of a pantothenic acid free ration to pigs resulted in a loss of appetite, lowered growth rate diarrhea accompanied by a severe enteritis, and a characteristic locomotor incoordination often referred to as goose stepping " One of the most characteristic pathological findings in pantothenic acid deficient pigs is a diffuse congestion of the large intestine with an excessive discharge of mucus The wall presents a thickened and edematous appearance Degeneration of the myelin sheath of the sciatic nerve is also characteristic of the deficiency

The fact that pantothenic acid deficiency could not only be produced using purified diets but also in diets made up of commonly used feed ingredients was demonstrated by our own studies (Luecke *et al*, 1949 1950)

Perhaps the most distinctive characteristic of pantothenic acid deficiency is the occurrence of locomotor incoordination as shown in FIGURE 1 Although the neurological changes are irreversible the animals will grow to maturity In severe cases however complete posterior paralysis results followed by death

Multiple B vitamin deficiencies The fact that deficiencies of niacin and pantothenic acid could be produced in the laboratory on diets of natural feeds led the Michigan workers to investigate the possibilities of vitamin supplemen



FIGURE 1 Locomotor incoordination due to pantothenic acid deficiency

tation of practical swine rations The results of this work (McMillen *et al* 1949) indicated that rations containing corn oats soybean oil meal meat meal alfalfa, and minerals could be markedly benefited by the addition of niacin, calcium pantothenate, and riboflavin The results of this experiment are shown graphically in FIGURE 2

In view of the above results it seemed likely that B vitamin deficiencies were [illegible]

Some of these pigs were purchased and brought in for study One pig from [illegible]

duction of mucus were found upon histological examination The average leucocyte count for the 80 deficient pigs treated was 36 000 cells per cu mm compared with a normal range of 16 000 to 20 000 cells per cu mm

Because of poor appetites injections of substantial quantities of the B vitamins were given intraperitoneally Doses of 50 mg thiamine, 50 mg riboflavin 250 mg calcium pantothenate 270 mg niacin and 10 mg pyridoxine were used In addition a 19 per cent protein ration supplemented with liberal amounts of the same vitamins used for the intraperitoneal injec

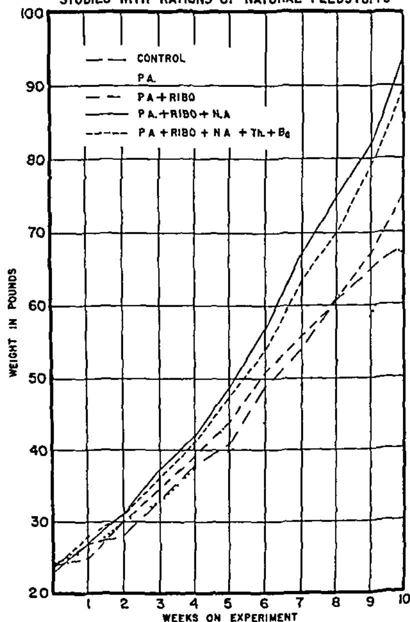


FIGURE 2. Growth response of pigs fed various B vitamin supplements. Note that niacin, calcium pantothenate and riboflavin supplements appear to be the limiting factors.



Fig. 88.3. Cecum, colon and stomach from pig showing symptoms of enteritis. Note thickening, heavy fold and surface exudate. The mucosa of the stomach was congested.

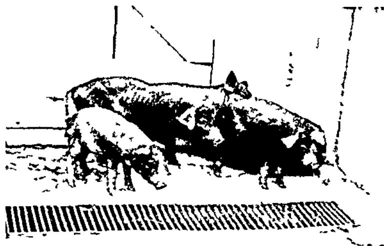


Fig. 88.4. A group of pigs showing severe enteritis before treatment. These animals were approximately [illegible]0 days of age and averaged 19 pounds body weight.

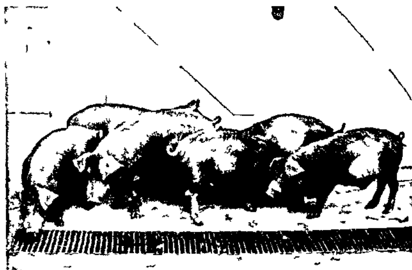


FIGURE 5 Pigs from the same group afer 3 days of treatment The animals a e aged 41 pound body weight

tions was fed The period of treatment varied from 30 to 40 days and resulted in the complete recovery of approximately 80 per cent of the animals treated

FIGURE 4 shows a group of pigs as they were brought in from a Michigan farm and FIGURE 5 shows the same group after 34 days of treatment

The results of these experiments demonstrate that a nutritional type of enteritis does occur under practical feeding conditions involving a multiple B vitamin deficiency Niacin and pantothenic acid however appear to be particularly involved

Antibiotics in the enteritis complex While all of the foregoing has demonstrated that deficiencies of certain members of the B complex are involved in the swine enteritis c ... f enteritis do not respond to v ... under farm conditic ... but rather a pathological condition caused by a number of factors Certainly the organism *Salmonella choleraesuis* belonging to the paratyphoid group is most frequently found in pigs with enteritis This same organism however is also frequently found in apparently normal pigs It thus seems logical i view of what is now known concerning the effects of deficiencies of certain members of the B complex on antibody production that a deficiency of one or more of these nutrients may be important predisposing factors

Whether the above is true or not remains to be determined However the recent use of antibiotics in the treatment of infectious enteritis where certain organisms of the paratyphoid have been found has had a remarkably beneficial effect in reducing mortality and morbidity A great many reports have appeared concerning the use of antibiotics for the treatment of enteritis The

method usually employed for treatment involves the addition of the antibiotic to the feed at levels of from 50 to 200 gm per ton If the animals are not eating significant amounts of feed, however, the method of choice appears to be by way of the drinking water This latter method is now used extensively

The use of antibiotics for the treatment of swine enteritis has virtually eliminated the disease, at least in certain areas where it was causing greater losses than all other diseases combined

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THE ROLE OF THE VITAMINS IN ANTIBODY PRODUCTION*

By A E Axelrod and J Pruzansky

Biochemistry Department School of Medicine University of Pittsburgh Pittsburgh Pa

Introduction Many researchers have been intrigued with the possibility of a relationship between nutritive state and resistance or susceptibility to infection As a result, the search for dietary factors that could influence the resistance susceptibility of a host to infectious disease has been prosecuted

graph attest to the mass of voluminous and often conflicting data in this field

The preponderance of efforts in these endeavors has been directed toward the possible relationship between diet and "natural" or innate" resistance Such investigations have been concerned with the ability of the host to survive the attack of a given virulent agent It is well known that numerous factors many of which are but poorly understood, may be involved in determining resistance to infection Therefore, by this operational procedure, the effect of diet is conditioned by the interplay of these various factors It would seem that a study of the delineated components of this complex phenomenon would offer promise of some interesting and perhaps useful information The classic antigen antibody reaction is generally considered to be a significant facet of this intricate mechanism It seems appropriate therefore to inquire into the interdependence if any between nutrition and antibody formation or actively acquired immunity A word of caution at this point it must be stressed that an immune response *may* not necessarily correlate with the degree of resistance to an infectious process

A review of the older literature in this field reveals an extensive volume of conflicting data with no *unequivocal* evidence to indicate that any specific vitamin deficiency invariably leads to impaired antibody production An accurate assessment of many of these earlier researches is difficult because of the questionable specificity of the deficiency under study, as well as the failure to utilize adequate inanition controls These studies have been summarized elsewhere by Axelrod and Pruzansky[1] The present paper will be confined to a discussion of our own experiments on the role of the vitamins in antibody response

Experimental Our investigations were designed to study systematically the effects of *specific* individual vitamin deficiencies upon antibody production in the albino rat In our first experiments human erythrocytes were employed as the antigen and the resulting serum antibody content was determined by the hemagglutination procedure More recently we have utilized purified diphtheria toxoid as the antigenic stimulus In this case serum antibody titer was determined by a hemagglutination reaction involving the use of

* These studies have been supported by a grant in aid from the National Vitamin Foundation Inc New York N Y

TABLE 1

SUMMARY OF THE DELETERIOUS EFFECTS OF INDIVIDUAL VITAMIN DEFICIENCIES UPON ANTIBODY RESPONSE TO HUMAN ERYTHROCYTES IN THE WHITE RAT

Severe	Moderate	None
Pantothenic acid	Thiamine	Vitamin D
Pyridoxine	Biotin	Vitamin B_1
Pteroylglutamic acid	Riboflavin	
	Niacin tryptophane	
	Vitamin A	

nic acid treated sheep erythrocytes coated with the diphtheria toxoid. efforts were directed toward producing individual deficiencies specific for vitamin under study. As controls, paired weighed, paired fed, and *ad libitum* fed rats were utilized. All control animals received the same diet as the corresponding deficient group plus the crystalline vitamin in question.

The early experiments with human erythrocytes as the antigen demonstrated that antibody synthesis was markedly impaired in certain vitamin-deficiency states. These results are summarized in TABLE 1, where it is evident that the most pronounced impairment of antibody response was noted in pantothenic acid, pyridoxine, and pteroylglutamic acid deficiencies. I wish to reiterate that identical immunological procedures were employed in all of these studies.

The failure of simple inanition to modify the antibody response has been demonstrated repeatedly in these studies. Further, no correlation between the inhibiting effect of a vitamin deficiency upon growth rate and upon antibody response could be shown. Thus, certain deficiencies, e.g., thiamine, caused very marked growth inhibition without greatly affecting antibody response. In other deficiencies, e.g., pteroylglutamic acid, a marked decrease in antibody response was noted, although the growth inhibition was relatively slight. This lack of any inanition effect in experimental animals is reminiscent of the observations made by Balch[3] and Gell *et al.*[4] in malnourished humans. Balch observed that prolonged nutritional depletion did not interfere with diphtheria antitoxin production in Schick-negative human subjects injected with purified diphtheria toxoid. Similarly, Gell *et al.* noted a relatively small difference in antibody production between well fed British soldiers and malnourished German civilians.

These observations are of interest in view of the tendency to associate inanition with a decreased resistance to infection. It should be pointed out that no evidence for the existence of individual vitamin deficiencies in their human subjects was presented by Balch and Gell *et al.* Thus it would appear that the inhibition of antibody response can be demonstrated only in specific individual vitamin-deficiency states comparable with those produced in the experimental animals. In this connection, Morey and Spies[5] have observed a decrease in antibody response to immunization with *Pasteurella tularensis* in patients with niacin, thiamine, and riboflavin deficiencies.

In order to investigate further the specificity of these vitamin effects, these studies were extended to include purified diphtheria toxoid as the antigen.[6]

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Biochemistry Department, School of Medicine, University of Pittsburgh, Pittsburgh, Pa.

Introduction. Many researchers have been intrigued with the possibility of a relationship between nutritive state and resistance or susceptibility to infection. As a result, the search for dietary factors that could influence the resistance susceptibility of a host to infectious disease has been prosecuted vigorously for many years. These studies have been motivated by the fervent hope that suitable manipulation of diet might influence the incidence and course [illegible] Other [illegible] to the more [illegible]

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the possible relationship between diet and "natural" or "innate" resistance. Such investigations have been concerned with the ability of the host to survive the attack of a given virulent agent. It is well known that numerous factors, many of which are but poorly understood, may be involved in determining resistance to infection. Therefore, by this operational procedure, the effect of diet is conditioned by the interplay of these various factors. It would seem that a study of the delineated components of this complex phenomenon would offer promise of some interesting and perhaps useful information. The classic antigen antibody reaction is generally considered to be a significant facet of [illegible] the

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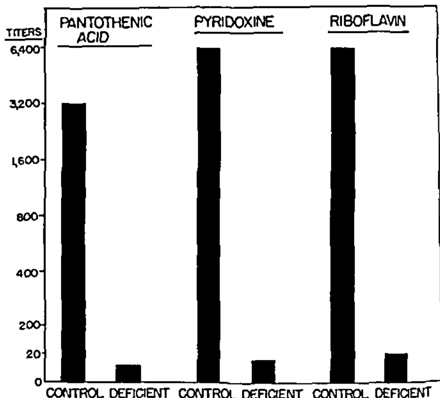


FIGURE 1. Circulating antibody production to diphtheria toxoid in vitamin deficient rats. Figures on the ordinate represent reciprocal titers.

With this antigen, a closer correlation could be drawn with the effects of the vitamin deficiencies upon resistance to infection. Again, individual deficiencies were produced in the rats and the animals immunized with the toxoid when a well defined deficiency state had been produced. Three weeks after immunization, serum antibody titers were determined as described above. The results are shown in FIGURES 1 and 2. The marked impairment of antibody synthesis in the following deficiencies is apparent: pantothenic acid, pyridoxine, riboflavin, biotin, and vitamin D. Not shown in these data is the marked inability of pteroylglutamic acid deficient rats to fabricate antibody. On the other hand, the thiamine deficient rats were fully capable of normal antibody synthesis. Not shown is the fact that good antibody responses were observed in many vitamin A deficient rats. Thus, these experiments demonstrate the extreme effects of certain vitamin deficiency states upon antibody production to diphtheria toxoid in the white rat. With the exception of the marked deleterious action of the vitamin D deficiency, the trends observed with diphtheria toxoid were similar to those previously noted when red blood cells served as the antigen. This difference in the effects of a vitamin D deficiency with the two antigens is interesting. Investigative pathways of this type may lead us

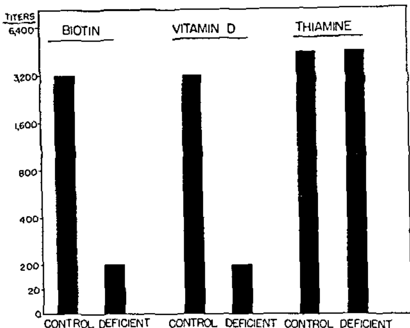


FIGURE 2 Circulating antibody production to diphtheria toxoid in vitamin deficient rats Figures on the ordinate represent reciprocal titers

to an understanding of the mechanisms of antibody synthesis and the precise role of the vitamins in this process

The effects of a lack of pantothenic acid upon the various phases of the anamnestic (booster) response to diphtheria toxoid were next considered The results are given in FIGURE 3 The primary response to the toxoid was obtained three weeks after immunization in the usual manner As previously noted this *primary response was low in the deficient rats and high in the con*trols At this time a booster shot of the toxoid was given and the secondary response was determined one week later In the deficient rats no secondary response was apparent Therapy with pantothenic acid during this secondary phase was ineffective in producing a response Therefore the mechanisms normally developed in the primary phase that are necessary for the establishment of a booster response fail to materialize when pantothenic acid is lacking In contrast the controls show a marked anamnestic response These data emphasize the need for an adequate intake of pantothenic acid during the primary phase if a booster response is desired The value of this observation in clinical practice remains to be determined

The concern of this laboratory with the interrelationships between dietary components and resistance susceptibility to disease led to an investigation of the effects of vitamin deficiency states upon serum complement which is recognized as an important factor in certain immune phenomena [6] The re

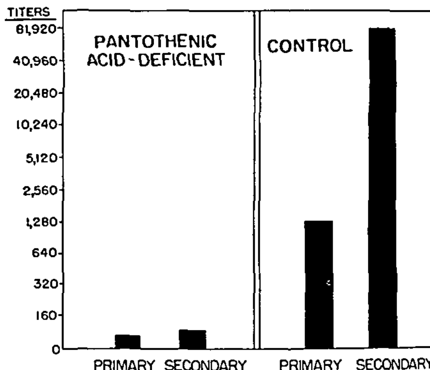
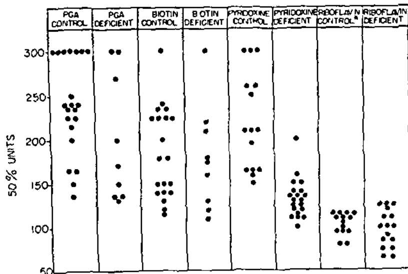


FIGURE 3 Anamnestic responses to diphtheria toxoid in pantothenic acid deficient and control rats F ures on the ordinate represent reciprocal titers

sults of this study are shown in FIGURE 4 A decreased level of compleme *was noted only in the rats deficient in pyridoxine and riboflavin* These e fects, however, could easily be attributed to the concomitant state of inanitic in these deficiencies The low complement titers of the riboflavin inanitic controls is evident This lack of a specific vitamin effect upon serum co plement was further demonstrated in a study of the rate of serum compleme regeneration in vitamin deficient rats[6] In this experiment, the serum co plement was depleted *in vivo* to a negligible value by the successive admin tration of Type 3 pneumococcal polysaccharide and the homologous rabb antiserum The rate of complement regeneration was then determined bo in deficient and control rats As seen in FIGURE 5, the deficiency states had significant effect upon serum complement regeneration

Discussion The need for certain vitamins in the biosynthesis of antibodi is clear What can be said about the mechanism of their action? Let us fir analyze the difficulties involved in attempting to answer this question W are asking for information on the role of biological factors concerned in th mechanisms of the synthesis of a protein when we actually know so little protein synthesis To complicate matters further, this protein is one whic is not normally present in the body but is fabricated mainly through the stim lus of a foreign protein With the recognition of these difficulties, I shou

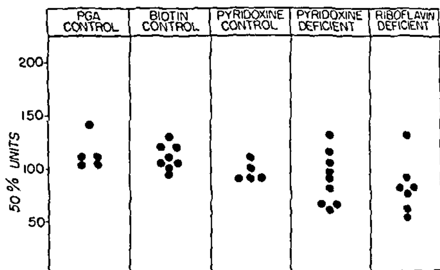


* Paired fed with riboflavin deficient group

Figure 4 Individual serum complement titers in vitamin-deficient rats

like to discuss some of our experimental approaches to this problem At this point it becomes apparent that we have been stimulated to study the relationship between diet and antibody formation by the belief that nutritional techniques may prove of service in elucidating the complex mechanisms of antibody synthesis

There are many factors that might influence the biosynthesis of antibody protein *First* there is the possibility that the metabolism of the antigen might be altered in the deficiency state Very little is known about the role of nutritional factors in antigen metabolism and we have only recently undertaken such studies with labeled antigens *Second* we must give consideration to the possibility that the antibody synthesizing cells whatever they may be are deranged in the deficiency state Such damage may be manifested either by structural changes demonstrable by histological techniques or by disturbances in functional activity Experiments in our laboratory have indicated a disturbance in the functional activity of splenic cells from pantothenic acid deficient rats immunized with diphtheria toxoid In studies conducted in association with Doctor Abram Stavitsky it was shown that splenic cells from immunized pantothenic acid deficient rats in contrast to those from normal immunized rats were unable to fabricate antibody when cultured *in vitro* or when passively transferred to normal rats With Doctor Leuchtenberger evidence was obtained that the mean DNA content of isolated splenic nuclei from immunized pantothenic acid deficient rats was lower than that from comparable controls These results may be interpreted to mean that the deficiency



*Complement Levels Attained 22 Hours After Third Successive Daily Depletion

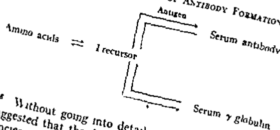
FIGURE 5. Serum complement regeneration in individual vitamin-deficient rats.

interfered with the acceleration of cellular division that normally accompanies antibody production in the spleen. Since cellular division is always preceded by an increase in DNA content, the participation of pantothenic acid in DNA synthesis becomes an intriguing possibility. *Third*, there is also the distinct likelihood that the vitamins, by virtue of their close interrelationship with various enzyme systems, function directly in the enzymatic reactions involved in antibody synthesis. Our complete ignorance of these reactions constitutes an effective barrier against any attempt to implicate the vitamins in specific enzymatic mechanisms. We do possess, however, a few bits of evidence bearing on this question. Our studies, utilizing electrophoretic measurements, have shown a normal serum gamma globulin content in vitamin deficient rats that are incapable of synthesizing antibody globulin.[7] If we accept the sche-

vitamin deficiency. *Finally*, it must be recognized that the serum antibody level that is utilized as a measure of antibody response probably reflects an equilibrium between the rate of antibody synthesis and release from the sites of synthesis on the one hand, and the rate of destruction of circulating antibody on the other. A change in any one of these factors could obviously affect the content of circulating antibodies. Thus, it becomes important to evaluate the effects of a vitamin deficiency upon antibody *release* and *degradation* before any positive statements can be made regarding any direct relationship between vitamins and antibody synthesis. We have carried out certain experiments in

TABLE 2

SCHEMATIC REPRESENTATION OF ANTIBODY FORMATION



this direction[8] Without going into detail we can state that the results obtained have suggested that the decreased level of circulating antibody in the vitamin deficiencies cannot be attributed to a faulty release mechanism or to excessive destruction of antibody It seems more likely that there has been a disturbance in the processes of antibody synthesis

Summary In conclusion, it can be stated that the data presented have demonstrated clearly that an antibody response can be markedly inhibited in various vitamin deficiency states We have made an attempt to indicate the research pathways we are following in our efforts to understand the role of these vitamins The possible application of nutritional techniques to studies in the biosynthesis of antibody has been pointed out In assessing the value of these observations to the relationship of diet to resistance to infection it must be stressed again that an immune response is only one facet of a complex mechanism determining resistance to disease The decreased immune response in a vitamin deficiency will obviously be significant in the phenomenon of resistance to infection *only* in those cases where the importance of antibodies has been definitely established

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Discussion of the Paper

DOCTOR KENNETH HETZEL (*Faculty of Medicine University of Adelaide Adelaide Australia*) Doctor Axelrod has presented in the work that he has been doing in recent years, further evidence of the relation between vitamin deficiency states and antibody production Like other people he has noticed that it is not inanition per se but the specific effect of vitamins in deficient supply that results in this deficient antibody production He did mention something that is new, and that is the effect of vitamin *D* on antibody response

to diphtheria toxoid that is the deleterious effect of vitamin D deficiency on antibody production He has mentioned that, in his work he is using red blood cells and diphtheria toxoid He mentioned also that in human beings Spies and others have found there was a deficiency of antibody production in response to the injection of *Pasteurella tularensis* in people with pellagra

There is some supporting evidence from the infection standpoint some work done in the Pathological Department of Columbia University by Zucker and by Zucker and Zorand who found that in young deficient rats *Corynebacterium* lethal to mice only killed off the rats in three weeks from infection The rats showed both pleurisy and pericarditis and multiple abscesses in various parts of the body

Then certain Italian workers working again on rats showed that *Salmonella typhosa* and *Brucella melitensis* again in pantothenic acid deficient rats failed to produce very good agglutinin responses whereas the animals on the same diet plus pantothenic acid showed very high titer to both of these organisms

Doctor Axelrod has stressed that measuring the resistance to infection by antibody response to injections represents of course, only one facet of this immune reaction Of course it does become of importance in clinical medicine when we use the presence of high titers to determine immune response in diagnosing diseases Also when we are watching the progress of an infection in the patient a rising titer does mean something of significance to us

It then would appear from this evidence that Doctor Axelrod has presented and from other evidence that the vitamins, especially of the B group seem to be definitely necessary in the elaboration of antibodies and agglutinins in the infections I have mentioned

These days in clinical medicine, I think probably most people expect too much of antibiotics and fail to realize that it is ultimately the cell of the body that has to deal with the infection That is the metabolism of the cell has to be such that it can produce what is necessary to combat the toxin, so that phagocytosis and other cell reactions can ultimately deal with the infection While the antibiotic does much in curtailing infection the ultimate conquest of the infection is through the actual body cell In view of this and of the increased metabolism under conditions of infection and the increased needs in all body cells adequate supplies of these vitamins must be given We have been doing that in clinical medicine for some time—I should say not entirely with the idea of speeding up antibody production but for controlling certain of the side effects that we have seen with antibiotics Antibiotics tend to disturb both production and absorption in the gut especially when administered via a gastrointestinal route So it becomes necessary at least to give the stated requirements of the vitamins, or even to give more than what is considered a normal requirement to the individual with the increased metabolism and under the conditions of stress

It was interesting that Doctor Axelrod generally found that the production of complement did not conform to the experiments on antibodies and that he thought perhaps the failure in reaction might have been explained by simple inanition I cannot give any opinion on that But, of course, it is still possible that there may be a member of the complex vitamin family that might be

responsible At the moment the one that seems so essential from work that has been described thus far in these pages seems to be pantothenic acid

I think too the work on the booster response to the diphtheria toxoid was extraordinarily interesting in that one does not get the booster response unless there is a primary response I am afraid I cannot quite say why that happened

DOCTOR ABRAM B STAVITSKY (*Department of Microbiology Western Reserve University Cleveland, Ohio*) In discussing Doctor Axelrod s paper I shall concentrate on the joint experiments that he mentioned briefly Many times during the day it has become obvious that it would be desirable to have more fundamental information on the basic aspects of both nutritional deficiency and antibody production Therefore, the experiments that have been described are the result of a very happy coincidence

For many years my laboratory has been engaged in studies of the basic mechanism of antibodies During the same period Doctor Axelrod has been studying the relationship of vitamins to antibody formation When he came to Western Reserve University several years ago it was quite natural therefore for us to plan experiments which combined the nutritional biochemical immunological techniques we previously had used independently

While the multidisciplined approach certainly has not solved the problem of the anamnestic reaction or of what nutritional deficiencies do I think it does offer a promising approach to a fundamental understanding of these problems

It might be helpful first of all to summarize the two experimental systems that Doctor Axelrod and I used Doctor Axelrod has mentioned the booster response This is the classical reaction study by Grennie and Sidnerson in England 20 years ago One gives toxoid There is a small rise in antitoxin If however about three weeks later one gives toxoid again there is an accelerated production of antibody reaching a peak in about 10 days or two weeks later We have taken cells in the middle of this anamnestic reaction We have done two things with these cells First we have cultured them and second we have made homotransplants as it were of them If one cultures splenic cells from a rat thus inoculated one finds that these cells continue to elaborate antibody *in vitro* If one takes these cells and transplants them at this time to normal rats the process of antibody production apparently continues in the normal animal What we have done then is this we have used simply both normal and pantothenic-deficient donors as a source of these cells and have compared the antibody response As Doctor Axelrod indicated we have found that whereas splenic cells from normal animals continue to elaborate antibodies under these normal conditions cells taken from pantothenic-deficient animals were active by neither method

The other approach to the problem was to take cells from normal animals and transfer them to pantothenic acid-deficient animals There was a very meager response upon transplant of normal cells into normal animals On the other hand unexpectedly there was a very good antibody response when one transferred normal cells from immunized rats to pantothenic acid-deficient animals The cells derived from normal animals were able to produce antibody in a deficient animal

I think it would be desirable at this point since we have made so much of

these experimental systems, to summarize rather quickly some of the evidence for the validity of the use of these systems for studying antibody formation. Actually, there is good evidence that synthesis of antibody occurs when tissues from immunized animals are placed in a suitable medium *in vitro*. I can summarize this evidence briefly as follows: disruption of these tissues by any means abolishes antibody formation. If one incubates these tissues at zero instead of at 37°C, for instance, or uses any inhibitors of oxidative processes such as cyanide, dinitrophenol, or arsenate, the antibody production is inhibited. Moreover, the sites of antibody production *in vitro* parallel completely the sites of antibody production *in vivo*. If one injects, we know the spleen elaborates antibody, and only the spleen is active among the tissues cultured *in vitro*.

Now to go over to the passive transfer reaction. Again there is considerable evidence that this passive transfer or homotransplant actually involves the synthesis of antibody, at least related to the synthesis that occurs in the intact animal. There are three possible explanations of the homotransplantation reaction that one could visualize. I think I neglected to mention just what the possibility of homotransplant is. When one transplants cells from immunized animals several days *after the transfer of these cells, the antibody appears* in the recipient animal. It can be shown that this is actual synthesis. One can visualize this as actual transfer of antigen, or antibody, or, finally, that it represents active synthesis. The transfer of antigen with these cells can be eliminated rather easily. One knows that if one injects a large dose of an antigen into an animal it takes several weeks before an appreciable amount of antibody results. Moreover, any of the disrupting methods that I just discussed in connection with the *in vitro* reaction will result in disruption of the transfer action as well. So you cannot damage the cells. If it were simply a transferred antigen this would not be expected. Interestingly enough, these cells must have the proper metabolic environment. You cannot transfer cells from one animal to another. As we just indicated, the transfer may be successful in recipients that are unable themselves to make antibody by virtue of X irradiation, administration of cortisone, immaturity, *etc.* In other words, a young animal that does not make antibody will nevertheless support the transfer. Finally, in pantothenic acid deficient animals, you can exclude passive transfer due to the transfer of antibody to the cells because you cannot extract enough total protein. You cannot extract enough gamma globulin from these cells to account for the amount of antibody that appears in the *recipient animal*.

appeared in the recipient animal. Moreover, if one administers a radioactive labeled amino acid to the recipient animal shortly after the cells are transferred, this amino acid is incorporated into the antibody that appears, whereas the amino acid is not incorporated in the passively injected antibody. Therefore, both of these methods appear to be a good measure of active antibody synthesis.

As Doctor Axelrod mentioned, and as I have mentioned, when we applied

hese techniques to the elucidation of the role of vitamins in antibody formation it was found that the cells derived from normal animals were active under these conditions whereas cells derived from pantothenic acid deficient animals were not active These results provide a good deal of evidence as Doctor Hetzel has suggested for the autonomy of the cells themselves In other words one could transfer cells from immunized animals in the individual in the environment where antibodies could not be made by virtue of deficiency X radiation etc yet these cells did lead to the appearance of antibody As to why the ransfer reactions occurred in deficient animals whereas they did not occur in ontrols the only reason I can give is the inability of the recipient to destroy transplanted cells since the pantothenic acid deficient animal makes anti oodies very poorly if at all When it comes to explaining Doctor Axelrod's results however I must admit that we are still far from correct and complete answers

Doctor Axelrod has given most of the obvious explanations of the effects of vitamin deficiency on antibody formation I have very little to add in this connection I do think however that the experiments with the cells in pantothenic acid deficient animals make it quite unlikely as Doctor Axelrod has already indicated that the inability of the deficient animals to make antibody is entirely due to their failure to release these antibodies

We were also completely unable to extract any antibody from the tissues You might say that the hemagglutination method that we employ is as far as I know the most sensitive *in vitro* method for the detection of antibody As 'ittle as 1/100 of a microgram or a thousandth of a unit of diphtheria antitoxin an be detected So if any active antibody is there we should detect it These ells did not yield any antibody whereas we could readily abstract such anti dy derived from the nondeficient animals The only other possibility that - wish to discuss is that there may be some disruption of the antibody synthetic mechanism in these cells Obviously it is too early to say that this is the reason but in this connection I think our experiments indicate some point of minor disagreement with Doctor Axelrod's indication that there might be some difficulty of conversion of a precursor to antibody The experiments we have done indicate that there is no appreciable amount of such a precursor in the transferred cells that in fact free amino acids rapidly find their way into the antibody Therefore if there is any precursor it does not accumulate but is turned over and converted to antibody very readily If Doctor Axelrod desires to change his word precursor to some sort of enzyme system or enzymes I can concur In any case I should think that the bulk of the evidence at this admittedly very early stage of information favors some disruption of the anti body synthetic mechanism in these cells In any event I think the possibilities of such systems for further study in fundamental mechanisms of antibody rmation and possibly in the other problem of protein synthesis are obvious

OBSERVATIONS ON INFECTION AND CERTAIN VITAMINS*

By Benjamin M Kagan

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Most observers find that severe deficiency of vitamin A is accompanied by decreased resistance to infection This appears to be true in spite of the fact that formation of specific circulating antibodies is not disturbed in vitamin A deficiencies, as shown so nicely in Doctor Axelrod s paper An example of an experiment demonstrating the influence of vitamin A deficiency was that re

about 80 per cent survived on an adequate diet[1] Similar experiments with mice and measured doses of mouse typhoid bacilli show differences in mortality rates of 80 to 100 per cent in the deficient animals, as compared to 10 to 20 per cent in the controls Doctor Frye has pointed out that, on vitamin A deficient diets fowl develop more and larger worms, and that the resistance of rats and dogs to ascariasis is decreased on vitamin A-deficient diets

A relatively long period of depletion is necessary before the influence of vitamin A deficiency on susceptibility to infection becomes significant This is most likely due to the fact that large amounts of vitamin A are stored in the liver An average human liver contains about 1,200 units per gram, or a total of between one half and one million international units of vitamin A[2] If all of this were available and at the rate of the recommended minimum allowance this would be sufficient to last the normal human for about three months Parenthetically, the infant, especially the newborn, does not have such a large store upon which to draw

In spite of this large reserve of vitamin A there is some evidence that its administration in excess of that contained in the average diet may have a beneficial effect on the course of infective processes Thus, Mellanby and Greene reported that the administration of vitamin A in amounts above that in the usual diet increased resistance to puerperal sepsis and septicemia[3] Ellis before the days of antimicrobial agents, found that vitamin A reduced the mortality of postmeasles pneumonia in a controlled series by 50 per cent[4] Donaldson and Tasher[5] also, in the same era, found that it reduced the mortality in a controlled series of adult patients with pneumonia by 44 per cent Other observers, however, have not been able to duplicate these results or to demonstrate increased immunity to infection as a result of the administration of vitamin A in excess of that provided in the diet[6-9]

One of the best controlled studies was that by Shibley and Spies[10] These investigators studied a group of students selected by random sampling No

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The author wishes to express his deep appreciation to his co-worker Doctor Elizabeth Kaiser for her assistance in all the experimental work cited. Doctor Kaiser is Research Associate in the Department of Pediatric Research Michael Reese Hospital Chicago Ill

subject knew to which group he belonged A careful record of respiratory infections was maintained One group received 200 000 units of vitamin A and 4 000 units of vitamin D per week Another group received 400 units of vitamin A The third group received maize oil The seasonal incidence of colds and their severity were alike in all groups The duration of colds however, was significantly shorter in those students who received the added vitamin A The later reported findings of Cameron[11] were similar

Information was sought therefore on the need for and the role of vitamin A during acute infection It has been known for some time that blood levels of vitamin A decrease during acute infection, in spite of the large amounts in the liver This has been observed particularly in pneumonia abscesses and acute rheumatic fever[12 14]

This suggested certain questions In the presence of acute infection is there an increased tissue demand for this vitamin or an increased utilization? In the absence of either of these where does the blood vitamin A go? Is absorption impaired? Is the rate of liver uptake and release different in the presence of infection? These are some of the questions which stimulated our experiments, which are still going on and which I am about to describe

Wintrobe s group and others[15 17] showed that injection of turpentine or of sweet almond oil into rats produced abscesses which resembled bacterial abscesses in their histologic appearance We therefore used these substances to simulate infection in rats and studied the vitamin A changes in the blood urine and tissues

Mature albino male rats of the Sprague Dawley strain weighing about 200 gm each were used Control animals were fed the same standard feeding as experimental animals There was no significant difference in the mean weight gain of the experimental and control groups during the period of study

TABLE 1 shows the effect of the abscesses on serum levels Bloods taken two days after the first injection show changes in the same direction though not as marked as those seen two days after the third and fourth injections Bloods taken seven days after a single injection may show further lowering than two days after injection though in some animals there is some recovery toward the preinjection level

These results are thus similar to those observed in bacterial infection in humans Since they may have been specifically due to turpentine per se rather than to the abscesses similar experiments were done using sweet almond oil (TABLE 2) The results with this oil are similar to those with turpentine

TABLE 1
SERUM VITAMIN A
Four Injections of 1 cc Turpentine in Rats at Weekly Intervals

Experimental / Control Group	N	Before	Mean [illegible] After 1 Inj	Mean [illegible] After [illegible] Inj
[illegible]	[illegible]	35 ± 4	11 ± 3	[illegible] ± 3
[illegible]	[illegible]	24 ± 3	20 ± 4	24 ± 2

TABLE 2

SERUM VITAMIN A

Two Injections of 1 ml Sweet Almond Oil in Rats at Weekly Intervals

	No rats	Serum vitamin A (Mean) (μg /100 mg ± S D)	
		Before injection	2 days after 2nd injection
Experimental	5	27 ± 10	13 ± 7
Control (not injected)	5	30 ± 8	29 ± 10

The next step was to determine whether absorption and liver deposition of the vitamin are decreased Blood levels following a standard orally administered test dose of vitamin A alcohol were therefore determined The test doses were given by gavage to experimental and to control animals in doses of 12,000 units per kilogram body weight Blood levels were determined before the test dose 3 or 6 hours later, and 24 hours later The animals were studied in groups of six These studies were done in different groups of animals at different intervals of time after the injections, two days after a single injection of turpentine, two days after a single injection of sweet almond oil, two days after a second weekly injection of turpentine, and two days after a third injection of turpentine

In all of these studies, there were no significant differences in serum vitamin A at three hours or at six hours after the test dose At 24 hours, however, the serum levels in the experimental animals fell lower than the serum levels in the control animals The 24 hour levels in the experimental animals fell to the same low levels as before the test doses The results of one such experiment are shown in TABLE 3 These data suggest that gastrointestinal absorption and liver storage were not modified by the abscesses That the 24 hour level in the experimental animals fell so low suggests that the liver stores are low

The concentration of vitamin A in the livers was then studied TABLE 4 shows that the mean weight of the livers of the experimental animals was not significantly different from that of the controls However, the liver vitamin A

TABLE 3

SERUM VITAMIN A

Four Injections of 1 ml Turpentine in Rats at Weekly Intervals
Effect of Oral Dose of Vitamin A Alcohol 12 000 i u /kg body wt
Given two Days after Fourth Injection

	No rats	Serum vitamin A) (μg /100 gm. ± S D)			
		Before 1st injection turpentine	Before dose vit A	3 hours after dose	24 hours after dose
Experimental	5	32 ± 4	17 ± 2	168 ± 34	14 ± 9
Control	5	37 ± 5	41 ± 6	203 ± 109	48 ± 5

TABLE 4
LIVER VITAMIN A
Three Days after Fourth Injection of Turpentine

	No. rats	Wt. of liver	Liver vitamin A	
		gm	µg/gm ± S.D.	µg/total liver ± S.D.
Experimental	6	12.0 ± 1.2	101 ± 11	1 092 ± 140
Control	6	10.9 ± 1.4	131 ± 16	1 406 ± 124

concentration and the total vitamin A content of the livers of the experimental animals were significantly lower than those of the control animals.

These findings are similar to those found in humans who die with infection. In the humans, however, there has always been the additional question of inanition during the infection which led to death.

It will be recalled that the test dose studies suggested that intestinal absorption and the mechanics of liver deposition during the simulated infection were not impaired. This suggested the question as to what the liver concentration would be if vitamin A were to be given in excess of that provided by the diet. Animals were therefore similarly injected and 24 hours before being sacrificed, they were given by gavage one large dose of vitamin A alcohol (12 000 units per kg. body weight). TABLE 5 shows that the concentration of vitamin A in the livers of these animals was higher and that there was no difference between the experimental and control animals. This confirms the impression that liver storage of vitamin A proceeds normally in spite of the simulated infectious process.

We now attempted to determine where the serum and liver vitamin A were going under these conditions. Determination of the vitamin A concentration in the central purulent portion of the abscesses, compared to the adjacent tissue and to the tissue of normal rats, revealed no significant differences. The vitamin A levels in these tissues were very low. The center of the abscesses had mean levels of 2 µg. per gm., the periphery 3 µg. per gm., the normal subcutaneous tissue 2 µg. per gm.

Studies of the vitamin A concentration in other tissues including the kidney

TABLE 5
LIVER VITAMIN A
Three Days after Fourth Injection of Turpentine and One Day after Oral Dose of 12 000 I.U./kg. body wt.

	No. rats	Wt. of liver	Liver vitamin A	
		gm	µg/gm ± S.D.	µg/total liver ± S.D.
Experimental	6	9.4 ± 1	206 ± 11	1 950 ± 193
Control	6	10.4 ± 2	203 ± 25	2 127 ± 455

TABLE 6

URINE VITAMIN A

Four Injections of 1 ml Turpentine in Rats at Weekly Intervals
Urine Collected for Three Day Periods Beginning Two Days after Each Injection

	No rats	Two days before 1st injection		After injections	
		Urine vol ml /24 hrs ± S D	Urine vit A µg /24 hrs ± S D	Urine vol ml /24 hrs ± S D	Urine vit A µg /24 hrs ± S D
Experimental	6	45 ± 10	6 4 ± 0 7	106 ± 38	42 7 ± 36 0
Control	6	52 ± 16	4 9 ± 3 3	78 ± 19	11 2 ± [illegible]

spleen and intestinal wall also revealed no significant differences between the experimental and control animals The mean value for vitamin A concentration in the kidneys, however, was more than twice as high in the experimental as in the control group, but the variation is so great that the difference is not statistically significant

The urine (TABLE 6) revealed much higher levels of vitamin A in some of the experimental animals as compared to levels before injection and as compared to urine levels of control animals However, because of the marked variation in urinary excretion of vitamin A in the individual experimental animals there is no significant difference in the mean Normally there is no detectable vitamin A in the urine of humans, whereas, in some patients with pneumonia appreciable amounts of it appear

[illegible]

scesses, however, there is a difference in that in the kidney vitamin A is increased, if anything, and not decreased Interestingly, Reichstein's compound L acetate has been reported[19] to lower the blood and kidney vitamin A of rats

[illegible]

humans that, in acute infective processes, both blood and liver vitamin A are decreased They show that some loss may occur through the urine, but that

[illegible]

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FLUID BALANCE DURING INFECTION WITH REFERENCE TO PROTEIN AND MINERAL METABOLISM ENZYME SYSTEMS

By Joachim Kuhnau

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Although reactions of water balance to infectious diseases may vary w dely according to the nature of the infective agent and the localization intens ty and course of the infection the statement is possible that changes in flu d

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and then may be excreted by urine and sweat thus causing a more or less severe state of dehydration On the other hand if a regime containing l beral amounts of salt is maintained during the course of infection large quantities of water may accumulate in the extracellular tissue gaps and the resulting water retention finds its expression in local or general edema The seemingly opposite phenomena of dehydration and water retention may thus be expla ned on the same basis the loss of intracellular water This loss is accompanied by a corresponding loss of cell potassium which finds its way into the blood plasma and the inflammatory exudates of the infected organism and subsequently is eliminated in the urine[4, 5] The fact that protein starvation too may result in either dehydration or edema depending upon secondary conditions and in losses of potassium[6] points to a common origin of the changes in water economy caused by infections and by a lack of protein Indeed metabolism in acute infections is marked by the well known phenomenon of toxic destruction of proteins that is independent of body temperature and nutrition and leads to increased nitrogen excretion if the diuresis is large or to a rise of nonprotein nitrogen in blood if kidney functions are poor[7, 7a] Destruction of proteins as well as dehydration is followed by liberation and leakage of intracellular potassium which is first accumulated in the extracellular fluid and afterwards excreted in the urine[8] The release from the cell interior of potassium equivalent to the destroyed protein frees another portion of cellular water which leaves the cell[9] These facts justify the conclusion that increased breakdown of intracellular protein is one of the ultimate causes of the water and potassium drain from inside the cells during infection and at the same t me raise the question whether the status of protein nutrition might have an influence on the course of infections and the accompanying changes in water and mineral balance

The intimate connection of the changes in protein metabolism with disturbances of water and potassium equilibrium during infections makes it necessary to trace the mechanism producing the fundamental protein catabolic responses of the host organism to infectious stimuli The complexity of this mechanism is best shown by the fact that protein starvation which is apt to accentuate the toxic destruction of proteins may have quite opposite effects on the course of

infectious diseases It is well known from the work of Cannon[10, 11] and others that lack of protein in food deteriorates the status of an infected animal by suppressing antibody formation and thus diminishing the resistance of the organism against infection This effect concerns exclusively the host's organism On the other hand there is ample evidence gained from European experiences during and after World War II that extreme protein starvation contrary to expectation does not increase but actually decreases the incidence of infectious diseases (with the exception of tuberculosis the morbidity of which obeys special laws) to a very considerable extent Incidence and mortality figures in typhus, typhoid fever diphtheria scarlet fever rheumatic fever and bacillary dysentery were greatly reduced by lack of proteins in food in Central and Western Europe during the years from 1944 to 1948[12, 13] and endemic outbreaks of some of the above mentioned diseases vanished spontaneously under these conditions In addition protein starvation increases resistance against infection with vaccinia[15] and Heine, who first described poliomyelitis mentions the fact that incidence of this disease is highest in children of well to do families This apparent contradiction may be explained on the basis of the assumption that protein intake influences the course of infections in two opposite ways—first by enhancing the defense mechanisms in the host which are mainly mediated by highly specialized proteins and second by providing the invading bacteria with the nutritive material necessary for growth propagation and invasiveness Protein deficiency may thus damage the host by withholding the building stones essential for formation of antibodies but may at the same time inhibit multiplication of microorganisms and synthesis of bacterial toxins The prevalence of one or the other of these two mechanisms determines whether lack of protein has a detrimental or a favorable effect on the infected organisms The complicated interplay of these two modes of protein action in the field of the host parasite relationship and their repercussion on water and mineral metabolism require a more detailed discussion

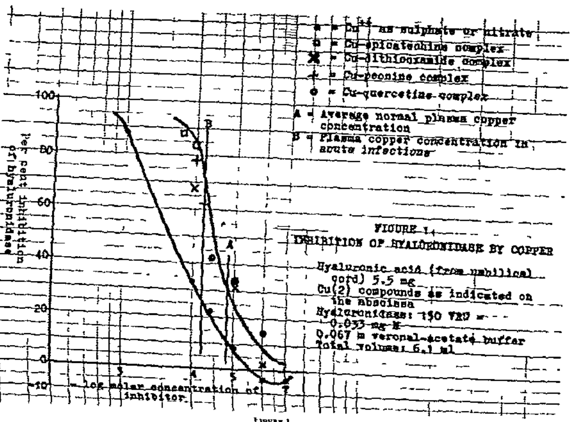
Protein economy of the infected organism as influenced by the parasite There is a great deal of experimental as well as clinical evidence that the invading parasite in generalized infections deprives the host of proteins or amino acids using them for its own growth and multiplication and that protein starvation stops microbiological growth by inhibiting this withdrawal of protein from the host This holds true for viruses as well as for bacteria Certain amino acids derived from the protein of the host cells are indispensable for growth of viruses and phages[16, 17] and lack or imbalance of amino acids is active either in suppressing the sequelae of virus infection at all or in mitigating its clinical course[18, 20] The tendency of viruses to accumulate amino acids or peptides at the expense of the host cell points to a competition for protein between virus and host[21] The linkage of virus particles to the cell surface is an enzymatic process catalyzed by a virus enzyme (amylase) and competitively inhibited by certain mucoproteins[22, 23] occurring *inter alia* in human milk[25] The protective action of human milk against neurotropic viruses may be of practical value[26] Gram positive bacteria (*Staphylococcus aureus*) are capable of accumulating amino acids within their cytoplasm against the concentration gradient to such an amount that the ratio of internal to external concentration lies between

10 (tyrosine) and 1670 (proline).[27] This accumulation of free amino acids is to be looked upon as the first step of protein synthesis. Gale and his co-workers have gained evidence that the process of intrabacterial amino acid assimilation and protein synthesis is the point of attack of many antibiotics. The accumulation of amino acids is inhibited by penicillin, the ensuing protein synthesis by chlortetracycline and oxytetracycline. The protein losses incurred by the host, brought about by these processes of fixation, growth, and multiplication of viruses and bacteria, are accentuated by the action of bacterial enzymes, which not only in themselves represent another kind of heterologous hostile protein but, in addition, act in propagating infection by destroying dissolved host proteins as well as membranes and other structural elements of the host cells. This deleterious effect, which manifests itself more or less exclusively at the protein matter of the host's organism, is brought about by protein splitting enzymes or proteaselike toxins. Among the numerous bacterial proteases, those of streptococcal origin have been studied extensively.[28, 29] In producing reactions of toxic protein breakdown, they are supported by the enzyme streptokinase,[30, 31] which combines reversibly with the plasminogen proactivator of the host's blood, thereby giving rise to a peptide splitting enzyme (plasminogen activator). This enzyme transforms plasminogen into the fibrinolytic enzyme plasmin.[32] Several peptides formed by bacterial proteases are themselves endowed with toxic properties of a hormonelike nature: the substances (leukotaxin, exudin, pyrexin, "LPP") producing inflammatory reactions in infected tissues are peptides.[33, 34] Simple peptides that may originate from toxic tissue proteolysis in infected areas exhibit permeability increasing properties, acting as pacemakers for the invading microorganisms.[35] Their action is supported by a great number of species specific bacterial hyaluronidases that enhance virulence and the spreading of bacteria[36, 37] by increasing permeability of the host cells, and that propagate inflammation phenomena (leukocytosis, fibroblast proliferation, formation of exudates and granulomas[38]). A direct relationship exists between hyaluronidase elaboration by streptococci and their virulence.[39] Whereas microbiological hyaluronidases are mainly produced by gram positive bacteria (micrococci, staphylococci, streptococci), gram negative bacteria are the sources of other enzymelike invasive substances with an enormous biological activity. These toxins which recently have been isolated from bacteria of the *Escherichia coli*, *Salmonella*, *Eberthella* and *Shigella* groups[40, 41] are protein bound lipopolysaccharides acting not only as highly effective pyrogens, but also by increasing membrane permeability and capillary fragility with the result of hemorrhagic necroses (Shwartzman phenomenon).[42] In addition, they induce certain host reactions such as leukocytosis, increases in phagocytic activity, and activation of the pituitary adrenocortical system. It is highly probable that the bacterial production of these catalytically active agents represents the essential humoral mechanism by which the well known response of the adrenal cortex to infections and the above mentioned toxic protein destruction in the host are mediated. All these effects are elicited by extremely low quantities of bacterial lipopolysaccharides (1 to 5 $\mu g/kg$), injection of 0.1 μg *E. coli* lipopolysac-

charide, corresponding to 10^{10} to 10^{11} molecules in an adult man, will produce intense pyrogen reaction, leukocytosis, and adrenocortical stimulation

Protein economy of the infected organism as influenced by adaptation reactions on the host side The most important protein-consuming reaction of the host to infectious stimuli, represented by formation of antibodies from gamma globulins, proceeds along two different lines If it is elicited by toxins that in themselves are of protein nature, it depends upon the action of adaptive enzymes created by the primary action of toxins (Burnet), whereas nonprotein toxins (*e g* pneumococcus polysaccharides) produce antibodies by direct template action (Haurowitz Breinl) in amounts surpassing the quantity of priming toxin by more than a million times However the protein requiring reaction of the host organism to bacterial or virus infections is not limited to antibody production from gamma globulins but, in addition, consists in a formation of a series of specific proteins and peptides, including members of the α_2-globulin group (haptoglobin) representing degradation products of mesenchymal glykoproteins [43] lysozyme,[44] some thermostable bacteriolysins,[45, 46] and a great number of nonantibody enzyme inhibitors directed against bacterial enzymes upsetting the host's protein and fluid balance by cell destruction or invasion The great variety of these inhibitors formed under the pressure of the chemical attack comprises a trypsin inhibitor of α_1 globulin character, a trypsin plasmin inhibitor in the α_2-globulin fraction,[47, 49] and several antiproteases that are also found in serum in infections and after injection of bacterial proteins [50, 51] These antiproteases (for the first time characterized by Abderhalden[50]) are not antibodies, since they can be produced by nonantigenic bacterial proteins (toxoids) Their relation to the other, mentioned protease inhibitors is still obscure Besides them, the infected host organism is able to elaborate a great number of antihyaluronidases that are partly heat stable and of a peptidelike structure, partly heat labile and true proteins Large amounts of both types of antihyaluronidases are present in the serum of subjects with acute infectious diseases, especially in pneumonia and rheumatic fever [52, 53, 54] The heat stable streptococcal antihyaluronidases are species and group-specific peptides, thus resembling true antibodies, while the thermolabile antihyaluronidases do not neutralize specifically the various bacterial enzymes The hyaluronidase inhibitors are of a special interest as regards water and protein metabolism in so far as the [illegible]

as a component of serum antihyaluronidase [illegible] the trace element copper takes part in the regulation of serum (plasma) antihyaluronidase activity, obviously by forming a copper protein complex with strong inhibiting quality Whereas ionized copper inhibits hyaluronidase only to a limited extent[58] and, in very low concentrations, even increases hyaluronidase activity copper in complex binding especially as a compound containing a vitamin P like substance (flavonol or anthocyanin) may reduce hyaluronidase activity very efficiently even at rather low concentrations[57, 58] (FIGURE 1) The inhibition of hyaluroni


• = Cu++ as sulphate or nitrate
□ = Cu-epicatechine complex
X = Cu-dithiooxamide complex
+ = Cu-peonine complex
⊙ = Cu-quercetine complex
A = Average normal plasma copper concentration
B = Plasma copper concentration in acute infections
FIGURE 1.
INHIBITION OF HYALURONIDASE BY COPPER
Hyaluronic acid (from umbilical cord) 5.5 mg
Cu(2) compounds as indicated on the abscissa
Hyaluronidase: 150 TRU = 0.033 mg N
0.067 m veronal-acetate buffer
Total volume: 6.1 ml
Per cent inhibition of hyaluronidase
100
80
60
40
20
0
-10
-log molar concentration of inhibitor
3
4
5
7

by 100 to 200 per cent The rise of plasma copper in infections may therefore be looked upon as an important defense mechanism against untoward effects of bacterial hyaluronidase

The phagocytic activity of granulocytes represents another type of defense mechanism operated by the host It depends upon protein intake in so far as the available body protein determines the absolute number of phagocytes as well as their state of ripening phagocytic activity being proportionate to the quantity of granulocytes and the degree of their maturation Phagocytosis itself consists mainly of a series of enzymatic reactions by which the membrane material and the cytoplasmic proteins of the parasite are stepwise degraded Phagocytes contain highly active proteases[65, 66] and peptidases of several kinds especially tri and dipeptidases[66, 69] Most of these peptide splitting enzymes display full activity only in the presence of cobalt[67, 68, 69] and there is some evidence that cobalt offered to the organism mainly as vitamin B_{12} plays a significant role in phagocytosis and defense against infection Indeed the almost complete disappearance of vitamin B_{12} from the urine in connection with moderately lowered serum B_{12} values* in patients suffering from febrile infections with leukocytosis (TABLE 1)[70] points to a definite tissue retention of this cobalt containing compound in infections and to an increased requirement for cobalt of the body during fever and enhanced phagocytic activ

[illegible]

ity of the leukocytic enzyme stores, which are greatly increased during infection This seems to be valid for serum peptidases too since most of them are also activated by cobalt

The degree of protein consumption brought about by the defense mechanisms against infection on the host s side must not be overestimated Although there is no doubt that food protein is needed for the compensation of the above mentioned [illegible]

[illegible]

metabolic adjustments (*vita minima*) probably hormonal in nature[77] and that it does not interfere generally with the humoral hematological and im

* The subnormal serum B_{12} levels contrast sharply with the highly increased B_{12} values in myeloid leukemia [illegible] interesting to note that phagocytic activity of leukocytes in this disease is abnormally low

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FORTIFIED BROAD SPECTRUM ANTIBIOTICS AS ADJUNCTS IN THE TREATMENT OF SURGICAL INFECTIONS OF THE YOUNG, THE AGED, AND THE DEBILITATED PATIENT*

By Aaron Prigot and Aubre de L. Maynard

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The introduction of the broad spectrum antibiotics in the treatment of surgical infections has placed in the hands of the surgeon potent anti-infective agents. Because the duration of the acute phase of such illnesses has been considerably reduced, a certain laxity in the total care of the patient has resulted.

It is to be remembered that once the acute phase of an infection has been overcome, the reparative process is still in operation and, in large measure, is dependent on the nutrition of the patient and on nutritional therapy. This latter factor is of even greater importance in the young, in the aged, and in the debilitated.

Since the water soluble vitamins are not stored, the disease process in itself disrupts the nutritional equilibrium by a reduction in the available nutrient factors through decreased absorption, decreased utilization, increased demand and increased loss of nutritional elements.

The decrease of nutritional elements available to the patient results from decreased intake, decreased absorption, decreased utilization, and increased loss. The loss of appetite produced by inactivity, fever, pain, general malaise, gastrointestinal lesions, and antibiotics causes a reduction in the available nutritional elements. Gastrointestinal lesions and special diets may also result in decreased intake.

Absorption of nutritional elements from the gastrointestinal tract may be decreased by disease of the tract or by alteration of the bacterial population of the intestinal tract incidental to the prolonged use of antibiotics.

In a large number of diseases, the efficiency of the liver is considerably impaired, thus preventing normal vitamin metabolism.

The increased nutritional requirements in stress have been thoroughly documented[1, 2, 3, 4] and this knowledge should be utilized in order to avoid such complications as secondary infections and delay in wound healing and convalescence. With elevation of the body temperature, metabolic processes are accelerated, and thus greater amounts of the nutritional elements are required.

Finally, the increased loss of vitamins through the various body fluids and exudates makes it imperative that a thorough supportive regime be instituted for the patient.

The role of antibiotic therapy in the treatment of surgical infections has been firmly established. In our hands, oxytetracycline and tetracycline† have yielded satisfactory results in the treatment of surgical infections, whether used alone or as adjuncts to indicated surgery.[5, 6, 7, 8, 9] They have shortened appreciably the clinical course of some infections and markedly reduced the

* This investigation was supported in part by a grant from Chas. Pfizer & Co., Inc., Brooklyn, N. Y., and the medication employed was furnished through the courtesy of this company.

† The trade names of Chas. Pfizer & Co., Inc., for the antibiotics oxytetracycline and tetracycline are Terramycin and Tetracyn, respectively.

incidence of surgical intervention Not infrequently, with the judicious use of these antibiotics, the surgical procedures were of lesser magnitude than are usual in such cases Postsurgical complications have been greatly reduced in cases in which the antibiotics were used either for the treatment of established infection or as a prophylactic measure

A brief review of the necessity for nutritional therapy in stress and disease and the proven worth of antibiotics in the prophylaxis and treatment of surgical infections indicate why a combination of vitamins and antibiotics would supply comprehensively the therapeutic requirements of the patient

The antibiotics employed in this study were oxytetracycline and tetracycline, available both in capsule form and in a suspension for pediatric use Each dose contained 250 mg of the antibiotic fortified with the following vitamins ascorbic acid 75 mg thiamine hydrochloride 2 5 mg riboflavin, 2 5 mg, niacinamide 25 mg, pyridoxine hydrochloride, 0 5 mg calcium pantothenate mg, vitamin B_{12} 1 mcg folic acid 0 375 mg, and menadione (vitamin K analog) 0 5 mg Adults received four doses daily and children proportionately less

The combination was well tolerated by all patients In no case were any side reactions observed, nor was withdrawal of medication necessitated by allergic or toxic manifestations The addition of the vitamins in no way altered the absorption of the antibiotic[10] The results obtained indicate no significant variation with the choice of antibiotic

All the patients made an eminently satisfactory recovery, with many recalcitrant infections being brought promptly under control The ease of administration of the antibiotic and the nutritional elements, at the same time reduced the number of pills taken by the patient decreased the number of medications to be administered by the nursing service, and decreased the incidence of failure by the patient to take the prescribed medication Despite

TABLE 1

THIRTY FIVE CASES TREATED WITH AN ANTIBIOTIC VITAMIN COMBINATION

Diagnosis	Number of cases	Age range (years)	Debilities
Infections			
Carbuncle	8	50-69	Diabetes
Cellulitis of arm	3	20-35	Drug addiction
Cellulitis of leg	3	54-65	Chronic myocarditis
Infected lacerations	3	60-69	—
Erysipelas	1	52-61	Chronic myocarditis
Human bites	2	12 14	—
Abscess	1	59	Diabetes
Axillary adenitis	1	60	Alcoholism
Cervical adenitis	1	50	Alcoholism
Stress			
Fracture of femur	4	31 59	—
Fracture of hip	3	58 81	Diabetes arteriosclerotic heart disease senility
Stress and infection			
Burns	3	1½ to 11	

malaise pain and other manifestations of severe illness the patients appetites and general condition were satisfactory Complications such as pulmonary infections decubitus ulcers and delayed wound healing were not encountered

Harlem Hospital draws its patients from a section of the population economically depressed and living in a densely populated area Hence they do not have the advantages of adequate rest sunlight fresh air and good nutrition Not infrequently on admission to the hospital they present in addition to the acute illness varying degrees of avitaminosis and malnutrition To no group of persons are the words of Pollack and Halpern[11] more applicable In orde to administer maximally effective therapy to all patients the physician mu t assume that all patients are somewhat nutritionally depleted



FIGURE 1 Se erely omm nuted fracture of the left h p (81 yea -old male) treated by open red tion and oxytet a yc ne tam n comb na on as prophylax s aga n t nfe on

The 35 patients chosen for this study presented problems either of severe infection or stress, or a combination of both The cases were selected from among *the young, the aged, and the debilitated* *The various types of surgical* cases treated are listed in TABLE 1

Twenty-five patients suffered from various surgical infections Nine cases were complicated by diabetes, six by chronic myocarditis, and three cases by drug addiction Two cases were human bites in teen agers, and three were infected lacerations in elderly people

The following case is typical of the latter group

Case No 1 J P, a 69 year old man, had sustained a severe laceration of the right forearm six months previously The laceration was sutured, but became infected and had continued to drain This patient was a diabetic on 60 units

FIGURE 2 Inter[illegible] fracture of the femur [illegible] year-old male [illegible] tetracycl[illegible] *employed to supplement nutritional therapy and for prophylaxis against infection*

of insulin daily The physical examination was noncontributory except for the severely infected laceration of the right forearm a culture from which revealed *Staphylococcus aureus* Within 72 hours after initiation of therapy the thick yellow discharge became thin and healthy granulations began to appear At this time excision of a necrotic tendon was performed and thereafter healing was uneventful

In cases of severe fractures in the aged where open reduction is contemplated and a relatively long period of immobilization of the patient is necessary we have found that the antibiotic vitamin combination is most excellent It acts both as prophylaxis against infection and at one and the same time supplies the daily vitamin requirement The medication is instituted before operation and continued as long as necessary



FIGURE 3 Infected fracture of the neck of the left femur (58 year old diabetic female) treated w h s ress fortified antibiotic Sinus tract injected with lipiodol

Illustrative of the good results secured in such cases are the following

Case No 2, J L, an 81 year-old male, fell out of bed injuring his hip

[illegible]

Case No 3 R H a 38 year-old male, was struck by an auto on April 11 1955 sustaining a dislocation of the shoulder, a fracture of the left femur tibia and fibula Open reduction of the fracture of the femur was performed and held in position by an intermedullary nail (FIGURE 2) Convalescence has been uneventful

Case No 4 A M a 58-year-old diabetic female sustained a fracture of the neck of the femur in 1953 She was treated conservatively, and the head of the femur began to undergo aseptic necrosis Two years ago, the area became infected and the patient developed a draining sinus (FIGURE 3) Under therapy, the patient has improved and the tract is now almost closed

The final group consists of three patients who have endured severe stress and in whom at the same time large portals of entry for infection have been established These patients ranging in age from 7 months to 11 years were

[illegible]

ing scalding with boiling water Physical examination revealed second and third degree burns of the abdomen and left thigh (FIGURE 4)

Case No 6 S M, an 11 year old boy entered the hospital on April 4 1955

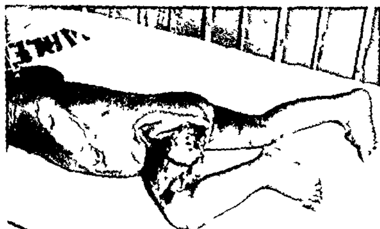


FIGURE 4 Seven month-old boy with burn treated with fortified tetracycline oral suspension

of insulin daily. The physical examination was noncontributory except for the severely infected laceration of the right forearm, a culture from which revealed *Staphylococcus aureus*. Within 72 hours after initiation of therapy the thick yellow discharge became thin, and healthy granulations began to appear. At this time excision of a necrotic tendon was performed and thereafter, healing was uneventful.

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FIGURE 3. Infected fracture of the neck of the left femur (58 year old diabetic female) treated with fortified antibiot... Sinus tract injected with lipiodol.

Illustrative of the good results secured in such cases are the following

Case No 2, J L, an 81 year old male, fell out of bed, injuring his hip

1) Convalescence was uneventful

Case No 3, R H, a 38 year old male was struck by an auto on April 11, 1955 sustaining a dislocation of the shoulder, a fracture of the left femur, tibia and fibula Open reduction of the fracture of the femur was performed and held in position by an intermedullary nail (FIGURE 2) Convalescence has been uneventful

Case No

neck of the

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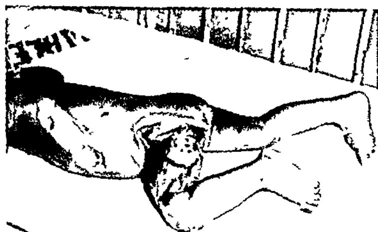


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In cases of severe fractures in the aged, where open reduction is contemplated and a relatively long period of immobilization of the patient is necessary, we have found that the antibiotic vitamin combination is most excellent. It acts both as prophylaxis against infection and, at one and the same time supplies the daily vitamin requirement. The medication is instituted before operation and continued as long as necessary.



FIGURE 3. Infected fracture of the neck of the left femur (58 year ol d abet c female) treated w th st fort ned ant b o c. S nus tract n ected w th l p odol.

Illustrative of the good results secured in such cases are the following

Case No 2 J L an 81 year old male fell out of bed, injuring his hip Physical examination revealed senility arteriosclerotic heart disease and a comminuted intertrochanteric fracture of the femur The fracture was reduced and held in position with a Smith Peterson nail and a McLaughlin bar (FIGURE 1 Convalescence was uneventful

Case No 3 R H a 38 year-old male was struck by an auto on April 11 1955 sustaining a dislocation of the shoulder a fracture of the left femur tibia and fibula Open reduction of the fracture of the femur was performed and held in position by an intermedullary nail (FIGURE 2) Convalescence has been uneventful

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Case No 6 S M an 11 year old boy entered the hospital on April 4 1955



FIGURE 4 Seven month-old boy with burn treated with for ed tetracycline oral suspension



FIGURE 5 Eleven year old boy with burn of chest treated with tetracycline vitamin oral suspension

after his clothing caught fire He sustained 15 to 20 per cent second degree burns and 1 per cent third degree burns of the chest and abdomen (FIGURE 5)

Case No 7 I H a 5 year old boy, was admitted on April 21 1955 having received a 2 to 3 per cent second degree burn and a 6 to 7 per cent third-degree burn of the right leg when his clothes caught fire (FIGURE 6)



F c ae 6 F e yea ol l boy w h burn trea ed w h te a y l ne tam n omb na on as an o al u pen on

Summary

The role of nutritional therapy in stress and disease has been throughly established The broad spectrum antibiotics oxytetracycline and tetracycline have proved their worth as adjuncts in the surgical treatment of established
[illegible]

In our experience the addition of the vitamins in no way interfered with the absorption and antibacterial action of the antibiotic The combination was well tolerated No allergic or si le reactions were observed
[illegible]

or infection or a combination of stress and infection These patients made rapid recovery with out complications of secondary infection delay in wound healing or retarded convalescence

The case of a lministration of the combination of vitamins an l antibiotic
[illegible]

C nclusi n

The combination of the antibi tics oxytetracycline an l tetracycline with vitamins represents a decided advance in the total care of the young the aged and the debilitated suffering from diseases involving stress an l infection

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Discussion of the Paper

DOCTOR W ADRIAN FREEMAN (*Department of Surgery, Harlem Hospital, New York, N Y*) I wish to thank Doctor Prigot for the privilege of reading and discussing his fine paper on supplementary vitamins in the infected and debilitated patient Many of the facts he has presented here have been observed on our service This is a well balanced study and will stimulate interest in the profession to study more thoroughly nutritional problems in health and disease

For many years at Harlem Hospital, we have given supplemental vitamins by mouth intramuscularly or intravenously, to all patients on the Fracture Service To name a few that have been used throughout the years brewer's yeast, hematinic capsules thiamine hydrochloride, B complex, vitamins A B D G, folic acid tablets, Berroca C, and injectable liver extract

Our patients are drawn from an overcrowded and economically depressed section of the city In addition to patients from the immediate area, we also receive indigent elderly patients from other hospital districts These patients do not have adequate diet, fresh air, or rest It is therefore inevitable that they are already suffering from borderline nutritional deficiency and secondary anemia

[illegible] fall from [illegible] Many [illegible] of time despite all our efforts for early ambulation The increase in the age of the general population is reflected in the large number of our patients who are over 50 years of age

Finally, many of our cases are admitted with many forms of ass[illegible] disease—diabetes generalized arteriosclerosis, peptic ulcers for example which have been long neglected because of economic factors

Harlem Hospital is a very busy hospital On our fracture wards we may have as many as 15 to 20 patients with severe fractures This throws a great strain on the nursing facilities The stress fortified antibiotics given [illegible] medication thus reduce the amount of work required from the nurses a[illegible]

[illegible]

assure the proper functioning of certain enzyme systems involved in the re[illegible]tive process

Doctor Arthur L Garnes (*Department of Surgery Harlem H[illegible] New York, N Y*) The comments made by Doctor Freeman concerning [illegible] are equally true of the plastic surgery service We see a large num[illegible]

[illegible]

ill, suffering from pain, general malaise, debility and loss of valuable [illegible] surface and body fluids These factors necessitate prolonged per[illegible] bed It is therefore of paramount importance that every available therapy [illegible] a supportive nature be administered in these cases We have found that the stress fortified antibiotics, especially stress fortified tetracycline as an oral suspension are extremely valuable in the treatment of our pediatric cases With the use of this combination, there have been fewer instances of secondary infection and no delay in convalescence The combination is well tolerated and thus we are assured that the patient receives and retains the medication

NUTRITIONAL AND METABOLIC ASPECTS OF INFECTION

By Laurance W Kinsell
Institute for Metabolic Research Highland Alameda County Hospital Oakland Calif

Many of the contributors to this monograph are vastly better qualified than I to discuss nutrition in relation to resistance and immunity to infection My remarks are confined to two fields (1) the place of corticoids* in resistance to infection in particular and stress in general, and (2) the relation of specific nutrients to pituitary adrenal function

Infection and the Pituitary Adrenal Axis

Four major sets of observations exist in regard to the place of the adrenal cortex in the over all picture of resistance to infection

(1) It has been well established that the resistance of the Addisonian patient or the adrenalectomized animal to infection in particular, and to stress in general, is markedly diminished [1]

(2) This resistance is changed very little in animals or humans maintained with desoxycorticosterone Maintenance with cortisone or hydrocortisone however, brings the resistance essentially to a normal level [2]

(3) Under appropriate experimental conditions, the administration of pharmacologic amounts of corticoids to experimental animals receiving inoculations of pathogenic microorganisms results in increased mortality [3]

(4) The combined administration of corticoids plus indicated antibiotics to critically ill patients under properly controlled conditions, appears to result in diminished morbidity and mortality [4]

On the basis of superficial evaluation, the above statements would appear to be confusing and contradictory Actually, when properly evaluated, they are neither (see below)

Established Physiologic and Pharmacologic Effects of Cortisone and Related Compounds

(1) *Regulation of energy metabolism* In the absence of the adrenal cortex, there is major impairment of neoglucogenesis, hepatic glycogen storage, carbohydrate oxidation, and, probably, fat oxidation [1 5]

(2) *Regulation of cardiovascular renal dynamics* In the absence of the adrenal cortex, there is progressive diminution in the blood volume, contractile power of the heart and glomerulotubular function [1] Corticoid administration corrects such abnormalities

(3) *Modification of the inflammatory reaction* Pharmacologic amounts of [illegible]

ficial or extremely dangerous (see below)

(4) *Inhibition of the effects of certain bacterial endotoxins* This effect appears

* The term cort co d s used in th s paper to include ACTH cort sone and hydrocort sone

to be well established [7] It is probably a major component of the over all "non specific antitoxic effect" of administered corticoids [4]

(5) *Inhibition of bacterial growth* Such an effect is not produced by any corticoid

(6) *Inhibition of specific antibody production* Under appropriate experimental conditions, such an effect can be demonstrated When corticoids are used *properly* in the management of infectious disease in the human such an effect either does not occur or is of such minimal degree as to be of no clinical importance [4]

Many other effects of cortisonelike compounds may play some part in the over all picture of resistance to infection The present discussion, however, will be limited to the above

The Use of Corticoids in the Clinical Man ig ment f Patients with Infectious Disea

There are three types of application of corticoi ls n su h patients

(1) *Replacement therapy in the patient with kn r n p tut iry or adrenal insufficiency*, i e, in the patient with Sheehan s syndr me r A l lison s disease In such individuals, one uses constant maintenance therapy the average dosage being 25 mg of cortisone acetate and 2 mg of buccal des xy corticosterone acetate daily, or 300 to 1500 μg of 9α fluorohydrocortis ne daily Such medication in the Addisonian patient produces a st ite of resista ice to infection comparable with the normal

When infection actually occurs in these patients the losage of corticoids must be increased, on the average, to 100 mg of cortisone daily or its equivalent Increase in the dosage of desoxycorticosterone is rarely required When the infection has been controlled with antibiotics the dose is gradually reduced to the preinfection level over a period of three to seven days

(2) *Prophylactic corticoid administration in individuals with suspected partial*

be in the form of infection, operative traum i thermal damage or the like That some individuals respond less well to stress than others is common knowledge Whether such differences in response at least on occasion may be the result of relative pituitary adrenal inadequacy is by no means clear It seems highly probable that this phase of the problem will be clarified during the next two years In the interim, one has occasion at times to answer the question 'Should John Smith, aged 65, who is less than a rugged individual, receive some supportive therapy to help him withstand a severe infection and or a major surgical procedure?" No unequivocal answer is possible at the present time It would seem to us however, that one might set up the following temporary "ground rules"

(1) Normally robust individuals should *not* receive supplemental corticoid therapy, except in the presence of dire and overwhelming emergency conditions (see below)

(2) In patients such as the John Smith noted above, the use of a modest dosage of corticoids, *e g* of the magnitude one would administer to an Addisonian patient exposed to stress, has little likelihood of producing harm, and may be of some real value (assuming that the patient has been well screened for the presence of contraindications to corticoid therapy) *Casual use of corticoids is contraindicated in any individual under any circumstances*

(3) *Corticoid administration in the presence of overwhelming infection* This [illegible]

circumstances, intensive corticoid administration, as the result of its antishock effect and nonspecific antitoxic effect, enables one to "buy time" until such time as the specific antibiotics have a chance to eradicate the offending organisms and the body has an opportunity to produce specific antibodies The standard emergency programs used in such patients are shown in FIGURE 1 The details of such therapy are discussed elsewhere[4]

Relationship of Specific Nutrients to Pituitary Adrenal Function

One would anticipate that relative or absolute deficiencies or excesses of specific nutritional factors would bear some relation to endocrine function Well known examples would be the changes in thyroid structure and function associated with iodine deficiency the change in functional activity of the β cells of the islets of Langerhans with variation in the relative and absolute concentration of carbohydrate in the diet, and the hyperplasia and hyperfunction of the parathyroids that can be produced by prolonged calcium and phosphorus deprivation

From the standpoint of response to stress, the importance of knowing the effects of specific nutrients upon the functional activity of the pituitary adrenal axis is of obvious importance

In FIGURE 2 is shown diagrammatically the relationship of some of the important exogenous and endogenous factors to the cell exposed to infection or other stress Nutritional entities play a double role Their availability in the proper amount is essential to the integrity of the body cells per se They are equally essential to the normal structure and function of the pituitary adrenal axis which in turn constitutes part of the major defense machinery of the body

One must preface any discussion of the relationship of specific nutrients to adrenocortical activity with the statement that the total body of knowledge is still far from complete The following statements, however, appear to be reasonably well documented

(1) *Sodium and potassium* are vitally concerned with the level of adrenocortical function sodium deficit or potassium excess exerting a stimulating effect and vice versa[1]

(2) A diet adequate nutritionally, but containing small amounts of *carbohydrate* and large amounts of protein, results in adrenocortical stimulation[1]

(3) *Protein deficiency* results in diminished adrenocortical function The adrenal cortices of protein-deficient animals, however, are normally responsive to exogenous ACTH[8]

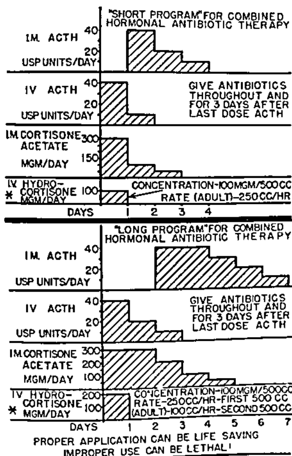


Figure 1 Standard hormonal antibiotic therapy The four-day program is used in more than 80 per cent of patients

enous ACTH [9]

Quite marked morphologic changes have also been demonstrated in the adrenal cortex in choline deficient rats during the period of active renal pathology. The adrenal cortex tends to return to normal as resolution of the renal pathology occurs [10]

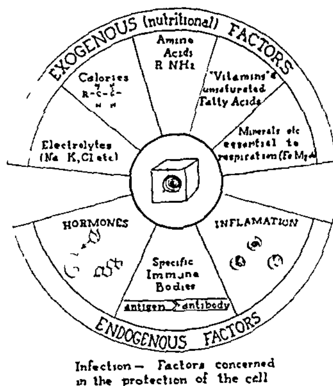


FIGURE 2 Exogenous and endogenous factors that condition the ability of the cell to withstand injury

(5) *Vitamin A deficiency* can be associated with a significant decrease in abi ity to withstand stress [11] It is still to be established whether cortisone will pro tect vitamin A deficient animals against the effects of stress

An increase in adrenal weight has been reported in rats fed large doses of vit min A [12] On the other hand, adrenal hypertrophy has been reported in th presence of vitamin A deficiency [13]

(6) Atrophy and reduction in the fat content of the adrenal cortex apparentl associated with impaired ACTH secretion, has been reported for rats wi *hypervitaminosis D* [14]

(7) The relationship of *vitamin C* to adrenocortical function is considerably less than clear The following points, however, appear to be established

(a) Under normal conditions, vitamin C is present in unusually high concen tration in the adrenal cortex [15]

(b) The cortical steroid content of the adrenals is markedly diminished in the scorbutic guinea pig [16]

(c) Scorbutic animals have adrenals which are markedly depleted in ascorbic acid but normally responsive to ACTH [17]

(d) There is some evidence suggesting that ascorbic acid improves the utiliza

tion of cortical hormones, and hence may decrease the requirement for ACTH stimulation under stress[16b, 18]

Whatever the final answer may be to the relationship of vitamin C and adrenal steroids, there would appear to be no question that ascorbic acid is not essential to a high level of adrenocortical function

(8) *Thiamine deficiency* appears to be associated with increased pituitary adrenal activity The magnitude is greater than that which occurs with simple caloric deficit[19]

with diminished ... luco corticoid adm

(10) Pantothenic acid deficiency results in reproducible histologic abnormalities in the adrenal cortex These changes are most marked under ... of acute stress[19b, 20] The mechanism of these changes and their ... significance is still unclear

(11) Pyridoxine deficiency is associated with diminished resistance ... but again, as in the case of riboflavin, it is still to be established whether attributable to a specific effect upon adrenal activity[21]

Nutritional Requirements During Intensive Corticoid Therapy

tion The special principles that apply to nutritional management under these conditions, center about some of the effects of pharmacologic dosage of the corticoids—namely, increased protein catabolism sodium retention potassium diuresis, disturbance in carbohydrate metabolism and the production of osteoporosis Consequently, the diet of the patient receiving corticoids is high in protein, relatively high in calcium and phosphorus low in carbohydrate adequate in calories low in sodium, and very high in potassium Since detailed

the normal requirement of all these entities

We have some observations that suggest that large amounts of nucleoprotein should be administered routinely to these patients This statement rests on

catabolic effects of the corticoids are exerted most particularly upon tissues with a high ratio of nucleus to cytoplasm (e g the thymus)

Whether the use of pharmacologic amounts of vitamin D will lessen the tendency to net calcium and phosphorus depletion is still undetermined In menopausal women and in older men anabolic steroids should always be coadministered to attempt to prevent such depletion

Intensive corticoid therapy should not be employed in patients with initially poor nutritional status unless such therapy is mandatory If corticoid therapy

is unavoidable (as in the case of fulminating periarteritis, dermatomyositis *etc*) prophylactic" broad spectrum antibiotic therapy should always be co administered in addition to the use of the nutritional program noted above The increased hypersusceptibility to infection that characterizes malnourished patients who are receiving corticoids is probably attributable to a variety of factors which include prominently the inhibition of the inflammatory reaction diminished production of antibodies, partly as the result of the increased protein catabolism (this statement applies *only* to malnourished patients) increased tissue edema with consequent tissue anoxia and diminished cellular resistance

Summary

The pituitary adrenal axis has been shown to play a major role in the individual s response to infection, as well as to other forms of stress A variety of nutritional factors are concerned in both a specific and nonspecific fashion, with the functional activity of the pituitary and the adrenal, as well as with the metabolic effects of the corticoids Until our knowledge in this field is more precise it may be well to accept the thesis that a diet is compatible with optimal ACTH and adrenal steroid production if high in protein, adequate in calories moderate in carbohydrate, and adequate in ascorbic acid and members of the B complex with particular reference to pantothenic acid

In the individual with increased endogenous adrenal cortical activity as the result of infection and even more in the individual with infection who requires supplemental corticoid therapy, it is of the greatest importance that full attention be paid to proper nutrition and antibiosis Under these conditions proper nutrition, in addition to the entities noted above, includes also limitation of sodium and intensive supplementation with potassium chloride

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Discussion of the Paper

DOCTOR MOSES M SUZMAN (*Johannesburg General Hospital, Johannesburg, South Africa*) In a consideration of the problem of nutrition in infections, one of the first questions to be answered is that pertaining to the susceptibility and resistance to infection in the presence of malnutrition In other words, is a malnourished individual more susceptible to infection than the normally nourished person, and, having contracted an infection is he less able to withstand it? All other contributors to this monograph have pointed out by animal experimentation that certain dietary deficiencies increase or diminish susceptibility to certain infections, thereby influencing resistance According to some investigators, this can be explained, at least in part, on biological and genetic considerations and characteristics of the particular species, or even of different strains of the same species So that, in my opinion, these findings on the whole can hardly be applied to man From experience with people suffering from frank deficiency diseases as pellagra, I have gained the impression they are not particularly susceptible to infectious disease and that they are able to combat infection once established—if not better than, at least as well as, normally fed subjects

I should like to illustrate this point by describing two cases of pellagra

The first patient was rather badly involved with pellagra, and he also happened at the same time, to have a very large postpneumonic lung abscess, as seen by X ray examination Despite this, he did not appear to be particularly ill clinically and he made an uneventful complete recovery in a short time on treatment with nicotinic acid and sulfapyridine It might have been thought that, having severe pellagra, his recovery would have been delayed, or that he might not have recovered at all His resistance had been poor The pellagrous lesions disappeared, or largely so He showed very severe pellagrous lesions on his face, lips nose, and eyes, and yet he withstood a severe infection indeed

The second case had deep lesions such as are found on the feet of pellagrins Despite being exposed to the infection of the roadway while walking barefooted the lesions of this patient failed to show any signs of secondary infections Cultures made from scrapings of the raw surface, which were deep and extended down to bone, were sterile

In nutritional deficiencies involving the B complex, endocrine glands and pituitary have been shown to be depressed, and it could be reasonably expected that systemic effects would be increased This is not the case One must explain the increased resistance and diminished susceptibility of the patient on the basis of lowered virulence of invading organism due to change of environment In other words in some dietary deficiency diseases, it seems that the essential nutrients lacking for the host's well being are also those that are needed to maintain the growth of invading organisms

It may be argued that, by correction of the deficiency of the host and inadvertently of the invader, the infective process would be encouraged It seems that this might be the test In other words, by improving the subject's nutritional state can his resistance to infection be increased?

To go further, one may ask whether, in a patient harboring infection and considered to be—or thought likely to become—nutritionally deficient, is it wise

or justifiable to prescribe essential dietary supplement without appropriate anti biotic coverage? That represents the symposium in reverse and cannot be answered but warrants future study

This leads to a more important problem namely, the influence of infection nutritional status of the patient Although it cannot be shown that malnutr tion favors infection since under certain circumstances it may even disc urag or prevent it there is little doubt that infection itself intensifies poor nutrition that is that it favors the development of dietary deficiency states

A 32 year-old Bantu male in August 1939, was admitted with very ex breathlessness, palpitation edema, and signs of advanced cardiac failure () examination he was found to have consolidation of the right si le of l l

dine, with improvement in the lung condition This case indi l cipitation of acute beriberi heart failure may occur in the t e infection especially in that, previously, he had been on an u a le u therefore was on borderline nutrition state

A young Chinese boy, aged 15 had advanced and severe failure for which no cause could be found At the time l c l l unknown cause The diagnosis of beriberi heart failure was n a le treated with thiamine hydrochloride, with marked diures s an l re few days later it was realized why he had fever as malar il found in the blood This was an example of a boy previ usly quate diet precipitated into acute beriberi heart failure by a lana

It can be seen therefore, that in the presence of borderline nu

acute d etary deficiency state and replacement therapy are id ate l l development of such deficiency may be anticipated however u l there re prevented by prior administration of vitamin supplements and extr nutric t especially when a borderline state of nutrition is suspected be ause t the l s tory of dietary inadequacy, the excessive consumption of alcohol poverty ll age or other causes

Other examples of acute nutritive failure precipitated by infections include tis and in some

ho at the onset sually insid ous

of nutritional deficiency syndrome unless preventive measures are adopted

The mechanism for the development of nutritional failure in the presence of infection can be explained, possibly on the basis that the invading organism depletes the host of its low stores of available nutrients also perhaps because the pat ent s level of metabolism has been raised by the infection thereby in creasing the requirements of essential nutrients beyond the body s available supply

This brings me to the last point which I want to discuss, namely, the hormonal status of the patient with particular emphasis on adrenal cortex, already referred to by Doctor Kinsell, with whose remarks I am in complete agreement

In the course of infections, although the inflammatory reactions—that is reactivity and production of immune bodies—are two essential protective mechanisms they do not always succeed in preventing irreparable damage to tissues or organs not infrequently, fatal results This damage is due not necessarily to direct destructive effects of the invading organism or its toxin, but to the continuing and persistent excessive reactivity set up by the host s tissues to a degree and extent far in excess of what ordinarily should suffice to withhold the ravages of the infectious agent In other words the reparative process itself may prove to be the lethal factor This heightened degree of inflammatory activity may occur despite the fact that antibiotics, in seemingly adequate dosage are being administered, and the identity and sensitivity characteristics of the causative organism are known

This ineffectiveness of antibiotic therapy is not necessarily due either to natural or acquired resistance of the causative organism to specific antibiotic agent or to insufficient dosage Some other intrinsic factor or factors must perforce exist through which are determined the degree and persistence of the tissue hyperreactivity as well as the accompanying exaggerated systemic and constitutional effects

From available data and from Doctor Kinsell's studies, it would appear that in some way the adrenal cortical function is involved There is either lack of hormone production or relative insensitivity of the inflamed tissue to existing amounts of circulating adrenocorticoids, amounts which in normal circumstances would be sufficient

Whatever may be the nature or cause of tissue hyperreactivity and the marked systemic manifestations so frequently seen in these severe infections the use of ACTH cortisone, or hydrocortisone and, more recently, of the delta 1 dehydrocortisone preparations, which, incidentally, have a very high anti inflammatory effect, will frequently succeed in affording sufficient suppression of these exaggerated reactions

Needless to say whenever possible, appropriate antibiotic therapy in adequate dosage and for a sufficient period of time must be used in conjunction with adrenal corticoid medication The latter, however, can be resorted to, if need be and relied upon as the main therapeutic measure when the specific antibiotic agent for the particular infection is not available or when the causative infectious agent has not been determined or is unknown For example, in various virus infections and other inflammatory diseases of unknown cause, when the life of the patient is threatened by an overwhelming or uncontrollable infection or from its complications adrenal cortical therapy should not be withheld on the theoretical grounds of the presumed consequent danger of the spread of the infection Under these circumstances the infection has already spread This applies no less to tuberculosis of the miliary, meningitic, or bronchopneumonic type than to any other type of severe infection It must be appreciated in regard to tuberculosis, that effective antibody coverage is fortunately available and this should meet any objection offered Besides, the principle is no dif

ANTIBIOTICS AND NUTRITION IN INFECTIONS

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There is a voluminous and conflicting mass of data concerning interrelations between antibiotics and nutrition in various infections, both acute and chronic Since the subject is of extreme interest from clinical and biological standpoints it seems worthwhile to appraise the known facts and to focus attention further on some of the lines of thought currently being pursued

All available data implicate the seriousness of vitamins K and B complex deficiencies that have occurred with prolonged use of chemotherapeutic agents and antibiotics These deficiencies could result from (1) elimination of intestinal bacteria that normally synthesize the vitamins K and B-complex group (2) the diarrhea and vomiting that may result from antibiotic administration or (3) the anorexia and subsequent diminished food intake that can result from the infection itself or from antibiotic therapy Thus, it is possible that in certain chronic debilitating diseases such as urinary tract infections, pulmonary infection, ulcerative colitis, bacterial endocarditis, tuberculosis osteomyelitis *etc*, where normal nutrition has already been threatened, further protracted antibiotic therapy could cause greater nutritional havoc Only during the past quarter of a century has our knowledge of nutritional therapy progressed beyond the empirical recommendation of a "nutritious diet" in certain debilitating diseases

A concept[1 2] of disease that emphasizes the phenomena common to all maladies irrespective of etiological considerations and that accounts, in part, for the nonspecific effects on metabolism that are essentially the same in all diseases whatever the nature of the primary etiologic factor, is concerned with stress This concept of disease describes a tripartite reaction—alarm, resistance, ex
... syndrome" and oc

cause of the dissemination of bacterial toxins, the febrile reaction, and the attraction of defense cells The defensive and reparative processes[3] that are mobilized whenever systemic stress is imposed are mediated by increased pituitary elaboration of adrenocorticotropic hormone (ACTH) which, in turn stimulates the adrenal cortex to elaborate its hormones, chiefly the gluco corticoids or antiphlogistic hormones These endocrine functions depend to some degree on the nutritional status of the individual Conversely, the results of endocrine action profoundly affect the absorption, utilization, and excretion of nutrients as well as the requirements for specific dietary factors[3] Body requirements may also be significantly increased by the increased metabolic demands Increased metabolism of carbohydrate to provide energy calls for an increased caloric intake and an increased intake of all nutrients concerned with carbohydrate metabolism[4]

It is desirable to provide sufficient carbohydrate capable of sparing pro-

some question as to whether a positive nitrogen balance can be restored by these means [7]

There is much experimental and clinical evidence to support a belief in the value of a high protein intake in conditions of stress [4]. As a corollary, it may be stated that those vitamins known to be of importance as units in enzymes concerned with protein metabolism must also be provided in increased amounts because of their greater utilization in this function [4]. These vitamins include riboflavin, niacinamide, pyridoxine, pantothenic acid, folic acid and B_{12} [4,13]. Thiamine and niacinamide play a role in carbohydrate metabolism and they are recommended in greater than normal amounts for use in acceleration of this function [14,15]. Because of the interrelationships between almost any two of the essential vitamins [15] it is probable that the optimal effect of a single vitamin given in large doses cannot be exerted unless the supply of all others is proportionally increased.

Both ascorbic acid[16] and pantothenic acid [7] appear to be essential in the metabolic functioning of the adrenal cortex. If their intake is not increased sufficiently during periods of stress, it is theoretically possible that response of the adrenal cortex may be impaired [3,4,5]. Various nutritional deficiencies, notably of ascorbic acid and pantothenic acid, may themselves constitute causes of stress.

The *in vivo* synthesis of essential vitamins of the B-complex group and of vitamin K is well documented [19,20]. In recent years there has been a growing realization that the commonly employed antimicrobial agents can interfere with the synthesis of the B complex vitamins and of vitamin K. Daft and Sebrell [3] have reviewed this subject as it related to the sulfonamides and have recorded many instances of vitamin K and folic acid deficiencies occurring in patients treated with these agents. Deficiencies of this kind resulting from the administration of sulfonamides have been observed in normal subjects receiving a normal diet, indicating that vitamin production in the body is important to its economy. Deficiencies have resulted from administration of other antimicrobial agents. Penicillin has resulted in the precipitation of niacin deficiency [24] and chloramphenicol in niacin, folic acid, B_{12}, and vitamin K deficiencies. Oxytetracycline and chlortetracycline have also resulted in deficiencies of vitamin K, riboflavin, niacin, B_{12}, and folic acid [25-27]. By replenishing vitamins in such drug induced deficiencies it has been possible in many instances to correct these manifestations [25-27]. What role this plays in the ultimate recovery from the infectious process in man is difficult to assess. *Ad hoc* reasoning would suggest that it is important.

In this preliminary study, we were interested in evaluating the clinical effectiveness, as well as any untoward reactions that might be encountered with *the combination of oxytetracycline and tetracycline with the water soluble* vitamins originally designated as Terramycin formula No 1 and Tetracyn formula No 1, now identified as Terramycin SF and Tetracyn SF respectively.

As anticipated (see TABLE 1), the addition of the water soluble vitamins did

TABLE 1
CLINICAL RESPONSE TO TETRACYN SF

Diagnosis	No. of patients treated	Average dose gm./day	No. of days treated	Response		
				Satisfactory	Indeterminate	Unsatisfactory
Acute pharyngitis and tonsillitis						
Streptococci	5	1.5–2.0	5–7	5		
Others	9			9		
Laryngotracheobronchitis (no culture)	2	2.0	5–12	2		
Pneumonia						
Pneumococcic	2	2.0	7–10	2		
Bronchopneumonia (no culture)	2			2		
Viral	2					2
Urinary tract infection						
S. albus	1			1		
E. coli	5	2.0	10–14	5		
Ps. aeruginosa	1					1
Proteus vulgaris	3				1	2
Soft tissue infection (*S. aureus*)	1	2.0	7	1		
Cellulitis (no cultures)	5	2.0	7–10	5		
Pyoderma						
One culture—*S. aureus*	3	1.5–2.0	8–10	3		
Soft tissue abscess (with I & D)						
S. albus	1	1.5–2.0	7	3		
S. aureus	1					
No culture	1					
Periapical tooth abscess (no culture)	1	2.0	14	1		
Total	45			39	1	5

not alter the clinical or antimicrobial effectiveness of the contained tetracycline. The responsiveness is comparable to our previous studies[28] with tetracycline alone and to those of other investigators.[29,30] It is to be noted that the viral pneumonias did not respond. Three patients with urinary tract infections, two with *Proteus* and one with *Pseudomonas aeruginosa* had received, on previous occasions, all of the broad spectrum antibiotics singly or in combination. The infecting organisms were resistant to all the broad spectrum antibiotics. One patient with a *Proteus* infection, however, had a successful clinical course, becoming asymptomatic and afebrile, and with a diminishing pyuria, in spite of persistent positive urine cultures for *Proteus* with demonstrable *in vitro* resistance to tetracycline. The patients with acute clinical illness resulting from either indefinable or sensitive pathogenic organisms responded satisfactorily within 24 to 48 hours. In these patients with acute illness, there was no incidence of a better response or of a better clinical status at the conclusion of therapy than would be expected with Terramycin or Tetracyn alone.

As seen in TABLE 2, 53 patients were given 1.5 to 2 gm. of Tetracyn SF for 5 to 14 days orally. In most instances, antibiotic therapy was indicated and in those patients who responded promptly, medication was administered over the indicated prolonged period in order to evaluate drug intolerance. Forty-nine of the patients had no untoward effects and four had complaints referable

TABLE 2
UNTOWARD EFFECTS OF TETRACYN SF THERAPY
Dosage gm 1 5–2 0 OD
Route oral
Length of time administered 5–14 days
Total number of patients treated 53

Results	
No adverse effects	49
Gastrointestinal complaints	
Anorexia	1 (day 5)
Anorexia and bulky stools	1 (day 8)
Nausea and vomiting	1 (day 3)
Abdominal cramps and eructation	1 (day 4)

to the gastrointestinal tract Two of these had mild anorexia and, in addition, one of these two had bulky stools starting on the eighth day This did not prevent continuation of medication and completion of therapy The two patients who had the more serious complaints refused medication The one patient with bronchopneumonia, who had abdominal cramps and eructation, was also receiving ammonium chloride as part of the regimen for congestive heart failure She refused all therapy at the end of the fourth day, but went on to a clinical remission It is our distinct impression that we dealt with a paucity of complaints in view of dosage and length of time of drug administration

Although acute vitamin deficiencies have been further implicated in the anorectal syndrome, thereby complicating antibiotic therapy, no satisfactory remissions have been observed with the use of vitamins in certain limited studies *It is to be noted in this present small series that the anorectal syndrome did not occur* This can be compared with the figure of 7 of 90 patients recently reported on a lower dosage schedule of tetracycline [32]

Whenever a clinical evaluation of the tetracycline group of antibiotics is made the untoward gastrointestinal effects are almost always well described In evaluating the recent literature on tetracycline, [28, 30-33] these effects have been of extremely variable incidence Theoretically, the irritable focus seems to be peripheral in mechanism Causative factors could be many, including alteration in the bowel flora, competition of the antibiotics with essential nutritive factors in the gastrointestinal tract, or specific drug allergy Specific drug allergy would appear to be of minor importance as, not infrequently, patients with almost the first orally ingested dose may become violent reactors Wood and his associates[31] demonstrated gastrointestinal side effects with parenteral tetracycline Sufficient medication could be secreted in the bowel to produce the complaints noted

A group of 10 patients (see TABLE 3) were treated with terramycin SF, 2 gm a day for 5 to 14 days Of this group two had untoward gastrointestinal effects

In comparing our preliminary results of tetracycline combined with the water soluble vitamins and previous studies with tetracycline alone, it would

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Streptococci	5	1 5-2 0	5-7	5		
Others	9			9		
Laryngotracheobronchitis (no culture)	2	2 0	5 12	2		
Pneumonia						
Pneumococcic	2	2 0	7 10	2		
Bronchopneumonia (no culture)	2			2		
Viral	2					
Urinary tract infection						
S albus	1			1		
E coli	5	2 0	10-14	5		
Ps aeruginosa	1					1
Proteus vulgaris	3				1	2
Soft tissue infection (*S aureus*)	1	2 0	7	1		
Cellulitis (no cultures)	5	2 0	7 10	5		
Pyoderma						
One culture—*S aureus*	3	1 5 2 0	8 10	3		
Soft tissue abscess (with I & D)						
S albus	1	1 5-2 0	7	3		
S aureus	1					
No culture	1					
Periapical tooth abscess (no culture)	1	2 0	14	1		
Total	45			39	1	5

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the indicated prolonged period in order to evaluate drug intolerance Forty nine of the patients had no untoward effects and four had complaints referable

TABLE 2
UNTOWARD EFFECTS OF TETRACYN SF THERAPY
Dosage gm 1 5—2 0 OD
Route oral
Length of time a lm n stered 5-14 days
Total number of pat ents treated 53

Re u	
No a lverse effects	49
Gastro ntestinal comp la nts	
Anorex a	1 (lay 5)
Anorex a and bulky stools	1 (day 8)
Nausea an l vom t ng	1 (lay 3
Al lom nal cran p s an l eru tat on	1 (lay 4)

l eart failure She refused all therapy at the en l of the fourth day, but went on to a clinical remission It is our distinct impression that we dealt w h a paucity of complaints in view of dosage an l length of time of drug adm [illegible] tion

Although acute vitamin deficiencies l ave been further implicated in the anorectal syndrome thereby complicating antil iotic therapy, no sat [illegible]

[illegible] testinal [illegible] parenteral tetracycline Sufficient medication coul l be [illegible] t p roduce the compl unts noted

A gr up f 10 patients (see TABLE 3) were treated w [illegible] gm a lay f r 5 to 14 days Of this group two had untow [illegible] ffects

In compari g our prel min ary results f tetracycl [illegible] water sol ble vitam ns an l previous stu l es with tetracy [illegible]

TABLE 3

UNTOWARD EFFECTS OF TERRAMYCIN SF THERAPY

Dosage 2 gm daily
Route oral
Length of time administered 5 14 days
Total number of patients treated 10

Results	
No adverse effects	8
Gastrointestinal complaints	
Nausea and milky stools	2 (day 4)

eem that a low incidence of significant untoward effects were noted In ecording all of these reactions, we encountered 7 per cent adverse effects of both positive and probable cause due to the medication

It is our impression that a higher incidence of reaction occurs in patients reated with Tetracyn or tetracycline alone than when combined with the water soluble vitamins A much larger series, however, must be investigated under comparable conditions If this should hold true, it would be of signifi ance in the prolonged therapy of such protracted disease states as ulcerative olitis, recurrent urinary tract infection, chronic pulmonary infections, bacterial ndocarditis, osteomyelitis *etc* The significance in these conditions where nutrition has already been threatened is apparent

Summary The combination of water soluble vitamins with tetracycline or oxytetracycline has been administered to 63 patients Preliminary findings indicate a lower incidence of side reactions, but this must be evaluated in arger series Whether or not the addition of vitamins contributes to the ultimate recovery of the patient and is a factor in the total body economy hould be further investigated

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NUTRITIONAL DEFICIENCY AS IT PREDISPOSES TO INFECTION AND THE ROLE OF VITAMIN DEFICIENCIES*

By Rubén Lopez-Toca†

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Since 1945, in association with Spies and Stone in Birmingham, Ala, and with García Lopez, Milanes, Diaz Tellechea, Reborado, and Aramburu in Cuba, I have been studying nutritional deficiences When I was invited to submit a paper to the conference on which this monograph is based the question immediately rose in my mind "What should my contribution be?" I decided that it should be none other than a discussion of the relationship between deficiency diseases and the incidence of infectious diseases in some of the patients we have been able to study over a long period of time

Introduction Time was when the field of nutrition involved little more than the question of prescribing a well balanced diet Since then, this field of knowledge has not only grown remarkably but has become an actual science as intricate and intriguing as any other branch of the absorbing complex of sciences that man calls medicine One of the most important recent steps made in the field of nutrition has been, in my opinion, the involvement of this field in other spheres of medical science This development by no means should be considered strange, as it has been impressed on the mind of every medical student at least since my earliest days at medical school, that a human being is an entity and that we must consider it in that light and try to solve its mysteries accordingly It is the invasion by nutrition of the field of infectious diseases that I shall consider in this paper Much notable work has been done in establishing the relationship between nutrition and infectious diseases but in my opinion it is the work of P R Cannon and his collaborators followed shortly by that of Berry and Spies and some others, using experimental animals, and that of Wohl and his co workers, on human beings that established the basis for well directed research in this field We have come a long way since then, and many additional facts of significance have been brought to light

One of the concepts in respect to the role of nutrition in infectious diseases on which much work has been done is that of antibodies Cannon and his co-workers[1] demonstrated that when hypoproteinemia is produced in experimental animals the production of antibodies is diminished This seems natural if we accept antibodies as globulins modified by the presence of an antigen These authors postulate antibody mechanism as the keystone of acquired resistance That the infant's resistance is greater in early life is something that has been observed by everyone and the reason for it is supposedly the protection conferred by the mother's antibodies at birth In 10 years of observation, Hess[2] verified that the incidence of pneumonia among 1200 infants under

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1 year of age was 3 times as great in those 6 to 12 months old as in those under 6 months of age. Studying 150 pellagrins Riddle, Spies and Hudson[3] found that *Staphylococcus aureus* and *Streptococcus hemolyticus*, isolated from cheilotic and ocular lesions, disappeared following riboflavin therapy. They noted also the disappearance of Vincent's organisms found in oral lesions under nicotinic acid therapy. They found in previously deficient patients, that the complement titer and bactericidal activity of the blood returned to normal levels as the diet improved. Berry, Davis and Spies[4] working with rats found a deterioration of various defense mechanisms in animals fed a diet similar to that of persons in an area of malnutrition. They did not test this diet in order to study isolated elements since single deficiency states seldom occur in Nature. In conclusion, they postulated the working hypothesis that resistance to certain bacterial infections may be depressed by inadequate nutrition. Patients with various diseases were studied immunologically and chemically, for antibody response in relation to dietary supplementation by Wohl, Reinhold, and Rose.[5] In 102 patients a common factor was hypoalbuminemia. These authors found an appreciable impairment of production of antibodies that was increased under dietary protein supplementation but the improvement was not enough to reach the titer observed in subjects with normal blood protein values receiving the same antigen stimulation.

Undoubtedly, proteins are not the only factor involved in antibody formation or in the general defense mechanism. There have been contributions to the literature on the effect of some blood cells and other body cells and of vitamins, minerals and caloric intake on these mechanisms. Lately it has been found that the complex action of the endocrine system will of necessity be linked with all these factors for the role of the system is integrated with the adrenal medulla, the hypothalamus, the anterior pituitary and the adrenocortex under stress situations. Moreover, some nutrients are required by the glands—vitamin C, for instance, by the adrenals.

Robertson and Tisdall[6] in an excellent work which has become a classic gave a diet made deficient in one nutrient at a time and a measured amount of *Salmonella typhimurium* to a group of rats and to a control group. In this experiment they proved that a low intake of a number of vitamins, a low intake of minerals, and a change in the quality of proteins can all lower resistance to infection. The increased susceptibility of animals deficient in vitamin A was mentioned long ago by Castellanos and Beato[7] who described the influence of the vitamin on fat metabolism, epithelial elements, opsonic index, and the reticuloendothelial system as an explanation of the protective action of the vitamin. Ten years after Castellanos, Leak[8] commented on some effects of vitamins A and D, as, for example, diminished body temperature immediately after injection and the decreased level of the blood in the presence of infectious phenomena, which he ascribed to the mechanism of visceral storage and not to their destruction as was supposed previously. Levenson *et al*[9] carried out a study based on the role of some vitamins and concluded that large doses of ascorbic acid, thiamine, riboflavin, and nicotinic acid may serve a useful purpose in the case of acutely ill people. Only a year ago Sebrell[9] stated that

the control of infections, of transmissible diseases and of materno infantile mortality, the decrease of which can be attributed at least partially to the improvement of nutrition, has resulted in a high longevity of the general population

Of course, not everybody is agreed on the defensive role of good nutrition in combating infections Contributions disproving this theory have been numerous, and we accordingly find papers emphasizing the fact that nutritional deficiencies augment resistance to infections and, on the other hand, other papers concluding that resistance is lowered when the nutrients in question are added to the diet

Schneider,[11] who ably explained these contradictory possibilities, summarized examples from the literature as follows the severity of *Plasmodium lophurae* infection in riboflavin deficient chicks is decreased and the severity of the infection in riboflavin deficient birds is increased when riboflavin is administered [12] An ascorbic acid deficiency in monkeys depresses the usual course of *Plasmodium knowlesi* infection, while supplementation with ascorbic acid results in increased parasitemia and death Schneider himself found in mouse salmonellosis,[14] that withholding fat from the diet results in increased *survivorship, and that adding fat results in decreased survivorship* He gives a final answer[15] to the conflict of opinions by saying that sometimes diet does not affect our resistance to infectious diseases, but that it has this effect chiefly *in the laboratory and sometimes in the outside world The vast bulk of the* experience of the outside world is that diet does affect our resistance to infections

Tuberculous infection, of course, has been a cause of dispute in connection with the action of nutritional deficiencies Many valuable works have appeared on this subject Getz *et al*,[16] for instance, have reported studies of a group of 1100 nontuberculous men observed over a period of years showing an incidence of 28 cases of tuberculosis These patients showed lower levels of vitamin A than the rest of the group

Ancel Keys[17] has stated that, in the case of tuberculosis, undernutrition seems to increase susceptibility and decrease resistance But for neither animals or man is there good evidence for decreased resistance or increased susceptibility to infectious diseases in general that may be attributed to undernutrition Where reasonable sanitation and epidemic control is maintained, infectious diseases other than tuberculosis present no special difficulties

Commenting on the argument that poor nutrition is accompanied by poverty poor sanitation, and poor housing, Tisdall[18] recalled that in Great Britain during World War II, housing deteriorated markedly while nutrition was at a higher level than before the war The prevalence of tuberculosis did not *increase to any appreciable degree In contrast, the Germans,* who long were considered to have a racial resistance to tuberculosis, have suffered since then not only from poor housing but also from poor nutrition and the incidence of *tuberculosis has soared Nutrition in postwar German* has had a profound effect on resistance to infection

About 15 years have elapsed since the fundamental works mentioned at

tools for work in this field and we hear new explanations of means used by the body to obtain energy from basic foodstuffs We even take into account new philosophical conceptions such as the ideas on resistance and susceptibility expressed by Schneider [1]

Materials and methods It is well to emphasize that what I describe is based purely on clinical observation of deficiency diseases in Cuba

The patients under study constituted a large contingent of undernourished people the majority of whom were patients with sprue and nutritional macrocytic anemia A minority comprised cases of pernicious anemia hypochromic anemia pellagra anemia of pregnancy beriberi and so forth in the order mentioned Vitamin deficiencies of every kind were present in the patients in the more complex cases their symptoms mingling with those of the main disease diagnosed There were cases of nutritional macrocytic anemia that also had signs of riboflavin deficiency and of thiamine deficiency One patient had sprue and pellagra and another was a chronic sprue case that developed anemia of pregnancy Most of the patients were underweight The records of the whole group were integrated with those of 180 patients whose records we took arbitrarily from our files The total comprised 123 males and 57 females their ages ranging from 14 to 84 years (for details see TABLE 1)

These patients were studied from many different points of view but only those aspects important to our present purpose will be considered here In addition to the history the physical examination and the usual laboratory and roentgen ray examination other procedures were used to study these cases in accordance with the clinical data recorded for each group As the complete records would be too long to list such data will be mentioned as needed

With a few exceptions all of the patients had a history of eating food that contained little or no animal protein Such a diet common in the rural areas

TABLE 1
NUTRITIONAL DEFICIENCY PATIENTS

Main diagnosis	Number of cases
Sprue	80
Macrocytic nutritional anemia	52
Pernicious anemia	10
Pellagra	6
Hypochromic anemia	14
Anemia of pregnancy	4
Beriberi	3
Ariboflavinosis	1
Sickle cell anemia	1
	180

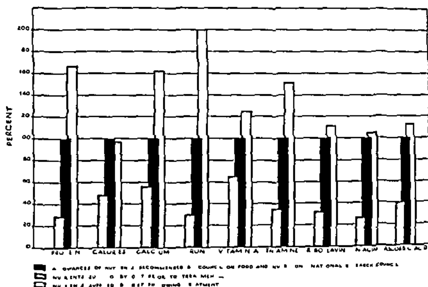


FIGURE 1

of Cuba, high in carbohydrates and fats, and low in protein and vitamins we regard as a factor of importance in the development of sprue (FIGURE 1). Many patients suffering from this disease were placed on such a diet and none developed a remission.[20] These foods were also combined in the same proportion as in the diets of the patients, then dried and fed to young white rats at a proper relative level of weight.[20] The rats had an arrested skeletal and somatic growth, priapism, testicular atrophy, arrested spermatogenesis, and alopecia.

Clinical signs of avitaminosis were present in no less than 80 per cent of the total number of patients, and a majority of them showed an appreciable loss of weight.

Serum protein levels were below normal in almost every patient, as formerly noted in a study of 121 cases of sprue,[21] of whom 80 per cent had total plasma protein levels of 6 gm. or below, 3 gm. being the lowest level.

In every case of sprue,[22] and in a high proportion of cases of nutritional macrocytic anemia, roentgenographic studies of the gastrointestinal tract with special search for nutritional disturbances, showed pernicious anemia, *and even in those malnourished patients with no specific clinical patterns* the symptoms were those of nutritional deficiencies.[23] These symptoms are intestinal segmentation with alternating intestinal spasm and dilatation, intestinal hypomotility, and signs of the "stack of coins" and of the "cog wheel." Even though these symptoms may be present in every disease that may produce submucosal edema, in these cases it is logical to accept the nutritional etiology.

A search for bacteria and parasites[24] of the intestinal tract was also carried out on material aspirated through a Miller Abbott tube and in material taken

by curettage from the intestinal mucosa by means of rectosigmoidoscopy Parasites were also looked for in the feces of every patient

Cardiologic investigations showed corresponding results in a few cases of beriberi[25] An electrocardiographic survey was made In 50 per cent of the cases of sprue,[26] we found low voltage and QT interval prolongation These

glucose tolerance tests, *etc* showed their results in accordance with every one of the diseases explored

From these data we have come to the conclusion that all of these patients were affected by nutritional deficiency diseases of many kinds Since one of

patients have developed later has been treated by us but the patients have received of course the help of other specialists in diseases other than those within the field of internal medicine This has offered us the opportunity of knowing what has happened to these people in addition to illnesses directly attributable to a nutritional deficiency which many of them have suffered for years with frequent relapses

Results Among our 180 patients many have had infectious diseases that occurred through the period of observation but only episodes occurring during relapses of their nutritional deficiency have been taken into consideration in the statistics herein given All diseases suffered in times when no symptoms or signs of nutritional deficiency were present have been ignored Minor infections suffered by everybody, such as the common cold, were not taken into consideration Under this plan, the following incidence was noted pleurisy 3 cases exudative pulmonary tuberculosis 8, pneumonia and bronchopneumonia 7 pulmonary abscess 1 sinusitis 3 urinary infection 1 bacillary dysentery 1, tuberculous lymphadenitis, 1 The total number of bacterial or viral infections 25 in number among the whole group of 180 patients represents an incidence of 13 8 per cent Analyzing the etiology of these infections we can divide them into two groups tuberculous and nontuberculous as in TABLE 2 and ascribing to the former group the cases of serofibrinous pleurisies whose etiology was demonstrated and 1 case of tuberculosis of the lymph nodes this infection reached a total of 12 cases or 6 6 per cent of the 180 patients analyzed Nontuberculous infections totaled 13, or [illegible] 2 per cent The distribution of these infections among the different deficiency diseases under study as may be seen in TABLE 3 showed no special predilection for any of them being more prevalent in those diseases having the higher number of cases even though pernicious anemia had a high incidence compared with that of nutritional macrocytic anemia cases

Intestinal parasitic ova cysts or adult forms were present in the feces of

TABLE 2

Infections bacterial or viral	Number of cases	Percentage of 180 patients
Exudative pulmonary tuberculosis	8	
Serofibrinous pleurisy	3	
Tuberculous lymphadenitis	1	
	12	6 6
Pneumonia and bronchopneumonia	7	
Sinusitis	3	
Pulmonary abscess	1	
Urinary infection	1	
Bacillary dysentery	1	
	13	7 2
	25	13 8

TABLE 3
DISTRIBUTION OF BACTERIAL OR VIRAL INFECTIONS APPEARING IN EVERY DEFICIENCY DISEASE

Main diagnosis	Number of infections
Sprue	14
Nutritional macrocytic anemia	8
Pernicious anemia	2
Hypochromic anemia	0
Pellagra	1
Anemia of pregnancy	0
Beriberi	0
Sickle cell anemia	0
Ariboflavinosis	0

61 6 per cent of the group, as recorded in TABLES 4 and 5, which shows a high percentage of intestinal parasitic infestation

Comments On reviewing the data collected, some clinical facts become more relevant as, for instance, the distribution of infections No special infection was observed In regard to the prognosis of infections in our patients it is to be emphasized that any patient admitted to the hospital with an infectious disease and exhibiting symptoms of a severe relapse of their malnourishment had a poor clinical course An example of this was a case of bacillary dysentery a patient who suffered from exitus letallis in spite of treatment, as did one of the cases of pulmonary tuberculosis, though it should be said that this was before the discovery of streptomycin and the newer chemical compounds so useful in the therapeutics of tuberculosis On the other hand clinical signs of augmented resistance to infections were exhibited by most of the cases when we had the opportunity of obtaining better nutrition for them Improved nutrition in addition to combating the infection, as shown by improvement of the general state and a decrease of the symptoms of infection was accompanied by reappearance of the appetite, an ascension of the weight curve, and disappearance of clinical symptoms of nutritional deficiency All this confirms, I think, the experience of all clinicians

TABLE 4
INTESTINAL PARASITIC INFESTATION

Number of cases	%
111	61.6

Parasites found
Ascaris lumbricoides
Necator americanus
Trichuris trichiura
Endolimax nana
Endamoeba coli
Strongiloides stercoralis
Giardia intestinalis
Chilomastix mesnili

TABLE 5
INCIDENCE OF INFECTIONS IN EVERY DEFICIENCY DISEASE

	Tuberculosis	Pneumonia	Sinusitis	Pulmonary abscess	Bacillary dysentery	Urinary infection
Sprue	6	3	2	1	1	1
Nutritional macrocytic anemia	4	3	1			
Pernicious anemia	1	1				
Pellagra	1					

Analysis of TABLE 2 shows an incidence of 13.8 per cent of infectious diseases in this group of 180 persons during a period of from 6 months to almost 10 years, the average period being 8 years. I have not the pertinent data to express the relationship of this percentage to that of a group of normal people of the same ages and general conditions, but if I were obliged to state my opinion, I should say that this percentage seems somewhat higher than that in normal persons. The incidence of nontuberculous infections resembles more or less that which occurs in normal people. Then the responsibility of the augmented general percentage is laid upon tuberculosis, which had a high incidence if we compare our figures with those appearing in statistics of the general population. In Cuba the incidence of this disease is 1.6 per cent according to the data I have been able to obtain. In the United States the incidence is calculated from 0.5 to 1 per cent. During World War II in the United States,[23] 18 million men were examined for military service and, of this total, 20.1 out of every 1000 were found to have some form of tuberculosis. About one third of those rejected had the disease in an active phase, which makes a percentage of 0.7.

Intestinal parasitism had a higher percentage than that found in a survey already mentioned carried out by Milanes and others of our group. The records of many of the patients studied by this group correspond in this respect to those of our present group of patients. All of our parasitized patients improved, as did those in the above mentioned group, under appropriate therapy, and the clinical signs of their deficiency disappeared. Their appetites

improved they gained weight, improved in other respects and, in the cases of anemia their blood reached normal levels All of this improvement followed despite the fact that no antiparasitic therapy was used In no case did the parasites disappear from the alimentary tract The hypochromic anemia cases showed also the same degree of improvement without treatment of the parasites

vation of

at higher

than that observed in normal persons

Infectious diseases having an etiology other than tuberculosis did not seem more prevalent in these patients than in other persons

Tuberculosis had a morbidity higher than in the general population

Clinical treatment proved more difficult in all infectious diseases when severe undernourishment was present and less difficult when nutritional treatment was added to specific therapy

Symptoms of nutritional deficiency disappeared under appropriate therapy despite the presence of intestinal parasitic infestation

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NUTRITIONAL PROBLEMS OF SURGICAL PATIENTS

By Jonathan E Rhoads and Charles E Alexander
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Cases of starvation in the United States at the middle of the 20th century are largely surgical Such nutritional deficiencies are rarely due to lack of available foodstuffs in the environment, but rather to a series of conditioned deficiencies in individual patients Thus, starvation may be conditioned by carcinoma of the esophagus or other obstructing lesions of the alimentary tract It may be due to the rapid growth of a tumor that parasitizes the food supply of the body It may be due to overactivity of the endocrine system, with elevation of the basal metabolic rate Acute infections with fever may step up metabolic requirements, or chronic suppuration may drain away protein, as in the case of surface burns or chronic draining sinuses Intestinal fistulas may shunt needed nutriment to the outside, or a deficiency of digestive enzymes may permit food to run its course through the alimentary tract unabsorbed and be lost in the feces Hypermotility with diarrhea may have a similar effect Such patients pass through a series of screening examinations, and many of them reach our surgical wards in the hope that obstruction can be relieved, fistulas closed, or suppuration controlled

While surgical methods can often help in obtaining these objectives, the immediate effects of preoperative treatment, of operation, and of postoperative care may tend to accentuate these deficits Furthermore, surgery in itself is a form of trauma, and it often precipitates the catabolic reaction classically described after long bone fracture by Cuthbertson and his associates in 1935[1]

The first three accompanying tables illustrate some of the nitrogen losses measured and reported in the literature I do not have comparable data for any of the other classes of food In the first are compiled data on preoperative losses,[2-9] in the second, losses of blood during operation, and, in the third, certain estimates of the further losses in the postoperative period

An important aspect of such cases is the interference with the progress of surgical patients that may result from protein deficiency Examples of this have multiplied, and half a dozen are listed in TABLE 4

Certain patients undergoing gastroenterostomy used to develop persistent vomiting due to failure of the new stoma to function The transfusion of such patients often changed the picture within a few days, so that gastric emptying was prompt

In the experimental laboratory, Mecray, Barden, and Ravdin[10] found an inverse relationship between the serum protein level of dogs and the gastric emptying time after gastroenterostomy Furthermore, this finding was not limited to fresh postoperative animals, but was found to obtain in some operated upon a year earlier and, finally, in nonoperated animals Roentgenologic observations by Barden revealed that the effect was not limited to the stomach but was manifested in the small intestine too, where the time for the head of the water barium meal to pass from the pylorus to the cecum was sharply increased by hypoproteinemia

TABLE 1

NITROGEN LOSSES IN VARIOUS TYPES OF SURGICAL PATIENTS

Losses Before Operation

	N loss	Period
	gm	*day*
Blee ing pept c ulcer (2	90 2	5
Thermal burn (2)		
Surface ooz ng	7 84	1
Total N loss	30 88	1
Small bowel obstruction (4)	11 04	1
Long bone fractures (1)	137 00	10
Long bone fractures (5)	190 00	Var able no weeks

TABLE 2

NITROGEN LOSSES IN VARIOUS TYPES OF SURG CAL PATIENTS

Losses Dur ng Operat on

Based on 3 gm of N trogen Per 100 cc of Blood

	Grams n trogen			
	M n mum	A erage		Max mum
			N o c	
[illegible]	15	24	4)	31 5
	3	12	(8)	21 0
	6	12	12)	21 0
	9	18	(3)	24 0
	13 5	36	(3)	42 0
	21	5	(16	108 0
	12	22 5	(10)	60

TABLE 3

NITROGEN LOSSES IN VARIOUS TYPES OF SURGICAL PATIENTS

Losses After Operat on

	N loss	Period
	gm	*day*
Hern otomy (8)	18 0	10
Subtrochanteric osteotomy (5)	65 0*	2 weeks
Gastr c resecti n (7)	54 0	5
Cholec stect my 8)	114 0	10
Gastri resect n (8	175 0	10
A ut appe l s (per ton tis 8	47 0	10
R p r (perf rated pept c ulcer 8)	136 0	10
Ra i al mast ct my 8	15 0	10

* A age of

[illegible]

TABLE 4
DEMONSTRATED DANGERS OF HYPOPROTEINEMIA

(1) [illegible]
(2) [illegible]
(3) [illegible]
(4) [illegible]
(5) [illegible]
(6) Decreased resistance to infection

levels by the administration of lyophilized dog plasma on the day the test wound was made led to prompt wound healing with a normal histologic appearance[12] Somewhat surprisingly, a similar effect followed infusions of gum acacia[13] It is not known whether this is a physical effect, or whether the acacia permitted the body to draw further on its attenuated supply of serum protein

Another effect of hypoproteinemia in dogs concerns the formation of callus *after experimental fracture of the ulna, as visualized by serial roentgenographs*[14] Whereas callus formation was virtually absent in hypoproteinemic dogs for 60 days considerable callus formation was evident in 39 days in the contralateral ulnas of the same dogs the following year, when proteins had been restored

It has long been known that chronically hypoproteinemic animals usually have reduced plasma volume, so it was not surprising that Ravdin McNamee Kamholz and Rhoads[15] found that hypoproteinemic animals required an average of only 26 cc /kg blood loss to produce a degree of shock that was brought about in normal animals by the loss of 45 cc blood/kg of body weight

Of particular importance today are experiments done on the relation of hypoproteinemia to resistance to infection Doctor Paul Cannon,[16] of the University of Chicago, showed that, in the rat, the build up of the antibody titer to sheep red blood cell antigen was sharply retarded in the *hypoproteinemic* animal and that restoration of this capacity required feeding com

ch as zein or gelatin

in patients were made at

hold, and Rose[17] where it

was demonstrated that the response was slower in hypoproteinemic patients *How general a phenomenon this is has not been demonstrated* It was of interest that many of the individuals suffering acute malnutrition in concentration camps during World War II did not succumb to infection but appeared to clinicians to be quite resistant Possibly, some natural selection of the more resistant individuals had already occurred by the end of the war, though this was not felt to explain the observations

Ross and Robertson[18] showed that the resistance of rats to a *Salmonella enteritidis* infection was lowered not only by protein deficiency, but also by certain vitamin and mineral deficiencies as well

There has been a considerable amount of work reported in the literature of the last 10 years on the question of a possible increase of infection among the malnourished Certainly, it has been a clinical impression for generations

that this occurs The British Medical Research Council[19] reported in 1931 that infections were greater in an African tribe that lived principally on cereals than in one in which there was a large intake of meat Benditt[20] has shown that two weeks on a protein deficient diet must elapse before hemolysin titers

ns
iver
pleen

Wainio[22] reported a decrease of several enzyme proteins in starvation with the exception of the cytochrome oxidases Work on such a basic level should prove fruitful in the future

In 1951, Schneider[23] questioned the general acceptance of the hypothesis that susceptibility to infection was increased by poor nutrition He stated

The time honored view that malnutrition decreases resistance has received some support, but is confronted by a substantial body of evidence in which malnutrition increases resistance Indeed for the *same* disease virus pneumonitis of mice, the *same* deficiency (pyridoxine) can operate *both* ways, depending upon its duration Metcoff[24] goes so far as to doubt an increased incidence of infection a poorer antibody production and an impaired bone marrow activity in undernourished rats Delaunay and associates[25] provide an excellent discussion and bibliography of how a deficiency state may diminish or increase the sensitivity of an organism to pathogens Chandler[26] has reviewed the problem in parasitism Schechter[27] reviewed the report of a team of physicians in Warsaw in 1942 He noted that there is not always an appreciable increase in epidemics of infectious disease in wartime starvation Community sanitation is said to be the controlling factor He contrasts the conditions in Warsaw and the clean cities of Holland and Austria

To consider a practical nutritional problem in clinical surgery one might think of a patient with a pyloric obstruction who might well reach a surgical service after a considerable weight loss due to anorexia and vomiting A period of gastric suction to empty the stomach of accumulated debris adds its bit to the process of starvation Then when operation is done, 500 to 1 000 cc of blood may easily be lost and the operation is capable of initiating a catabolic response of considerable proportions Unless methods capable of correcting this deficiency are brought into play the anastomosis may fail to function the wound may possibly dehisce, and various infections may supervene a sequence of events that complete a sort of vicious circle, as these complications tend to interfere further with nutrition

In an effort to see what correlation there might be between hypoproteinemia and post operative infections we have reviewed the charts of a series of general surgical patients at the Hospital of the University of Pennsylvania, Philadelphia Pa The basis of selection of the cases for study is shown in TABLE 5 The lower limit of normal taken was 6.3 gm of protein per 100 ml , and the series was divided into a normal ' control group and a hypoproteinemic group on this basis (TABLE 6) The infectious complications are grouped as wound, urinary tract respiratory tract and miscellaneous Noninfectious complications were not considered The incidence in each category is shown in per

Table 5

Postoperative Infections and Hypoproteinemia

Hospital of the University of Pennsylvania

Criteria for selection of cases	
. . . . . .	
	138
	11
Those not operated on, etc	25
Patients included in analysis	102

Table 6

Postoperative Infections and Hypoproteinemia

Hospital of the University of Pennsylvania

Criterion of hypoproteinemia—serum protein (s p) < 6 3 gm /100 ml

No of patients in hypoproteinemic group	42
No of patients in control group (s p > 6 3 gm /100 ml)	60

Table 7

Postoperative Infections and Hypoproteinemia

Hospital of the University of Pennsylvania

Classification of infections	Control group	Hypoproteinemic group
	%	%
Wound	15 0	28 6
Urinary tract	0	14 2
Respiratory tract	0	9 5
Miscellaneous	1 7	9 5

(Multiple sites of infection in the same patient were counted separately in this table only)

centage for the two groups in TABLE 7 It must be emphasized that this was not the incidence of complications among all patients but merely among those who had serum protein determinations recorded and who met the other requirements for inclusion in the series

The statistical analysis of these data is shown in TABLE 8 using only those cases with clearly defined infections and those who seemed clearly unafflicted with infection *The chance of the correlation between low serum protein and infection being unrelated* was less than one in 1,000 (TABLE 9)

Unfortunately, there was an intermediate group of patients who ran excessive fever or leukocytosis or both, who were suspected of having an infection but in whom this never became manifest

Even if we assume that all of these in the control group were infected and that all in the hypoproteinemic group were uninfected the probability that the correlation between the two groups is due to chance remains less than one in 100 This is set forth in TABLE 10

TABLE 8

POSTOPERATIVE INFECTIONS AND HYPOPROTEINEMIA

Analysis of Results

	No. of patients
Control Group	
(A) No infection	44
(B) Possible infection	6
(C) Definite infection	10
Total	60
Low Protein Group	
(A) No infection	12
(B) Possible infection	7
(C) Definite infection	23
Total	42

TABLE 9

POSTOPERATIVE INFECTION AND HYPOPROTEINEMIA

Chi square Values and Probability of No Difference Between the Groups

	No infection	Definite infection	
Control	44 (33.98)	10 (20.02)	54
Low protein	12 (22.02)	23 (12.98)	35
	56	33	89

Chi square 29.166, probability < 0.001
( ) Indicate predicted values
n = 1

TABLE 10

POSTOPERATIVE INFECTION AND HYPOPROTEINEMIA

Chi square Values and Probability of No Difference Between the Groups

	No infection	Definite & possible infection	
Control	44 (37.05)	16 (22.95)	60
Low protein	19 (25.95)	23 (16.05)	42
	63	39	102

Chi square 8.2[illegible], probability < 0.001
( ) Indicate predicted values
n = 1

While these figures would indicate quite strongly that a correlation exists how can we interpret such a correlation? Does the hypoproteinemia lower the resistance to infection? Does the infection lower the serum protein? Are both changes likely to occur from one or more common causes, such as extent of pathology, extent of operation, length of anesthesia or the like? We attempted to reduce the chances that the infection lowered the serum protein

level by dropping out cases in which infection was known to exist prior to the protein determination, but it is not possible to eliminate subclinical or prodromal stages of infection

In general, hypoproteinemia and infection tended to be more common among patients requiring the more extensive surgical procedures We cannot attempt to interpret the significance of the correlation found among the data We believe that, to conclude from them that the hypoproteinemia was the etiologic factor responsible for the infection would not be valid even though eventually, it may be shown to be true

In discussing these data one may well ask why so much attention is focused on serum protein concentration as opposed to total circulating albumin, estimates of antecedent protein loss, *etc* Serum protein concentrations were selected because they were available on many charts, whereas the more refined measurements had not been made often enough to permit this type of study

From a practical standpoint, restoration of nutritional deficits in surgical patients is of paramount importance

In too many of these cases, the oral route is not immediately available because of local disease or recent operation on the alimentary tract Preoperative correction must usually rest on intravenous methods and after operation, these may often be supplemented by feeding through tubes placed in the jejunum either directly (jejunostomy) or through the stomach (gastrojejunal feedings) The experience of Riegel and her associates[28] would indicate that food was a little more effectively used enterally than parenterally Transfusions of whole blood and plasma still play a basic role in the correction of hypoproteinemia and should not be lost sight of, especially as means of correcting the most pressing deficits of many of these cases of conditioned protein deficiency among surgical patients

Mineral and vitamin deficiencies may be hard to recognize but, as a rule, they are easy to correct by the intravenous route when the oral route is not available

Summary

Severe undernutrition is frequent among patients referred to surgical clinics

Operation tends to accentuate protein deficiency There is some experimental evidence that protein deficiency lowers certain of the defenses against certain infections

The incidence of infectious postoperative complications is correlated with serum protein concentrations below 6 3 gm /100 ml The probability of this correlation being a matter of chance is less than 1 per cent in the series analyzed *It is not possible to say from our clinical observations, however, whether the reduced protein concentrations are causally related to the higher incidence of infectious complications*

The effect of hypoproteinemia is to increase the chance for a variety of operative and postoperative difficulties

It is thus of tremendous importance to find ways of giving surgical patients sufficient foodstuffs by the simplest routes available, to supply their unusual

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CERTAIN ASPECTS OF DEFICIENCY DISEASES OF THE TROPICS AND TREATMENT OF SOME RELATED INFECTIONS

By Elmer H Loughlin and William G Mullin
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A surprising panorama of food deficiency diseases has unfolded in the tropics and, consequently, the importance of the classic deficiency diseases has gradually waned in most areas The symptom complexes arising from an insufficiency of food are considerably more inclusive and far more widespread than such restricted deficiencies as beriberi, pellagra, scurvy, and rickets They may vary according to the kind, degree, and duration of the insufficiency from mild latent conditions through progressive stages to extreme inanition on the one side and severe protein malnutrition on the other, or they may have overlapping gradients from inanition to protein malnutrition They are influenced by age and sex, by certain anthropological factors, and by such stress factors as pregnancy, lactation, and intercurrent infection, as well as by geographical location They are so intricate and diverse that they might have been woven by Arachne, and so inclusive that they might have been contrived by Dido

Until recently, these broad syndromes were scarcely noticed by workers in the fields of nutrition and tropical medicine, whereas deficiencies presumably caused by the lack of single factors received emphatic attention during the

of other vitamins, an even larger number of medical papers appeared However, scientific facts then had replaced speculation and fancy It would be improbable today that the term "protein" would be conferred on a district similar to "Limehouse" in London, nor is kwashiorkor heralded as a "menace" in banner headlines of today's newspapers as pellagra was in the newspaper headlines of 40 years ago, although protein with its amino acid components and associated factors, is certainly more important, and kwashiorkor more ravaging, globally, than pellagra

Although interest in the problems of tropical nutrition has been awakened

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sick, and that their lives usually are regulated by traditional customs and by religious and tribal taboos and superstitions It should be appreciated also that anthropopsychic disorders, resulting from malnutrition in early life, parasitic infections, and subsequent endocrine disorders, contribute to their backwardness, their seeming low order of intelligence, and the underdevelopment of the regions in which they live, and that this apparent inferiority should not be considered solely dysgenic

Since the notion that the fetus is merely parasitic and develops more or less

independently of its mother was discarded, it is now becoming evident that interrelated anthropological factors infections, and malnutrition also affect the unborn child long before it takes its first breath Thus, like specters, these factors haunt it virtually from conception through a toilsome, inglorious, and fast withering life to the grave If it were possible, it would seem timely at this point to inquire of the human zygote of the tropics, *Quo vadis?*"

Although it is essential to consider the reciprocal dependence of anthropological factors, infections, and malnutrition as causative of tropical deficiency syndromes from the prenatal period onward it is nevertheless fundamentally important to consider the maternal arc of the nutritional ambit before progressing to those of the infant and child Furthermore, since the mother is an integral part of the tropical community except for appreciable differences during early childhood, pregnancy, and lactation she is influenced by the same factors that affect other adults in the same environment Therefore, to provide an easier comprehension of the maternal role in tropical nutrition as well as to avoid duplication the aforementioned factors and their effects on adult tropical indigenes will be evaluated collectively and the notable exceptions as they pertain to the mothers will be mentioned or described briefly

The native tropical mother already may be gravely depleted by nutritional privation accentuated by overwork and parasitic infection and therefore, is physically unprepared to take on the ever growing burden of pregnancy and lactation In the face of increased nutritional demands by pregnancy and lactation the tropical mother, unlike many of her temperate zone counterparts seldom gets a special supplementation of her diet and instead certain high quality foods are made unavailable by seasonal deficiencies or may be interdicted by taboos

35 to 56 per cent of the League of Nations standard[3] and in many impoverished parts of Asia Africa Central America and the West Indies, they are equally low [4,10] On most of the Pacific islands where the traditional diets consist of fish bananas, breadfruit taros sweet potatoes yams, fruit, green vegetables and cocoanuts there is little evidence of deficiency diseases [11] In certain regions of Central America although the diets of the children may be markedly deficient both in calories and protein the diets of the adult agricultural workers who grow their own food are comparatively adequate Calorie, total protein calcium iron thiamine and niacin requirements are met, but intakes of animal protein vitamin A riboflavin and ascorbic acid are much lower than recommended [9]

Since rice is the staple food of more than half of the world population and supplies at least 70 *per cent of their daily calories it is undoubtedly the foremost cereal* In India China and Southeast Asia the daily diet is based on rice but foods of animal origin are negligible In other countries of the tropics rice may be completely or partly replaced by legumes maize and root crops In some countries it is grown in limited amounts and may be saved for special

feasts while, in others it may be imported and therefore, may be too expensive to include as a staple of the diet [12] In regions where rice is the staple of the diet, malnutrition is prevalent, and it is in these places that nutrition can be materially improved through the use of supplementary foods such as milk [4] The methods of preparation of rice for eating are also vitally important from the nutritional aspect Because of the peculiar harvesting and storage practices, rice is the only cereal that is regularly washed and cooked in water before it is eaten Ranganathan *et al* found that losses from raw rice due to washing and cooking amounted to 15 per cent of the calories, 10 per cent of the protein 75 per cent of the iron and 56 per cent of the calcium and phosphorus [13] while Swaminathan[14] found that up to 85 per cent of the thiamine also was lost Although rice enrichment programs have been successful in reducing beriberi substantially in certain parts of the Philippines where this deficiency disease was prevalent, they are considered by some investigators to be impracticable for large scale application [15]

Food plants in different parts of the world may vary considerably in biological value Dean has noted that maize, which usually has a low lysine content and a lysine methionine ratio usually of 2 3 in Guatemala has a still lower content of methionine and the ratio accordingly is 4 2 [16] In most areas of Central America maize is not only low in lysine and methionine but is especially low in tryptophane The deficiency of the latter amino acid accounts principally for the low biological value (usually below 50 per cent) of maize [10] Fortunately it has been possible to develop new genetic varieties, some with adequate tryptophane and niacin contents as well as reasonably adequate methionine content [17, 18, 19]

Moreover, in the regions where total intakes of protein are low, this deficiency usually is aggravated by exceptionally low intakes of animal protein although it is appreciated that high quality protein alone is not a substitute for an adequate quantity of total protein In China, there is only 5 gm of animal protein available daily per capita This figure is matched by that of 9 gm in India and 4 gm in Java and Madura [3] Similar low intakes of animal protein are the rule in many parts of Africa, Central America, and the West Indies [6 to 20 21 22] In a survey of four Nigerian tribes Nichols[23] calculated that one tribe—the Dakarkerri—consumed daily only 2 gm of animal protein per capita They offset this low intake of protein of good quality, however by consuming a large quantity of vegetable protein, 85 gm per capita daily Another tribe—the Isokos—consumed only 46 gm total of protein daily per capita 20 gm of which was of animal origin Incidentally hepatomegaly was noted in 9 per cent of the Dakarkerris and in 19 per cent of the Isokos and 3 per cent of the former had ascariasis while 31 per cent of the latter were found to be infected with this parasite In some parts of Africa, cattle are considered as measures of wealth and except for special feasts, are not slaughtered for food In many other parts of the tropics, the peasants [illegible] he cattle and seldom use them for their own food requirements [illegible] s and along rivers and lakes, where fish are eaten animal pr[illegible] tein intakes are much higher and deficiency diseases are l[illegible] [6, 7] In rural areas where transportation faciliti[illegible] e hc[illegible] n except occasionally

for imported expensive salt or dried fish. Pond culture of fish is being attempted in some countries to eliminate this inadequacy.

In parts of the tropics, the live weight of cattle does not exceed 450 to 500 lb and the output of milk during a seven to eight months lactation does not exceed 145 gal. Where better supplies of milk are available, peasants usually prefer to sell the milk when possible while, in other regions, because it is so highly contaminated, severe gastrointestinal infections frequently result from feeding it to infants. In some areas, according to Davies,[20] it is given to some adults as a luxury food, and the idea that children, and pregnant and lactating mothers require extra food is alien to African concepts. In still other areas, no milk is given after weaning.[23] A formidable obstacle in some countries where milk is available is its cost, and in those countries where it is distributed free to mothers and children, it can become a serious financial burden to the government.[10] The substitution of dry skim milk has been attempted. Deficiencies can result, however, when such milk is the principal or sole food of the infant (*vide infra*).

Dean[24] has observed also that in East Africa, food habits have changed in some parts because local supplies of certain foods have become exhausted, and that changes in agricultural schemes are brought about by the discovery of a new preference, by necessity, or by the completion of a government agricultural plan. He recommends that a famine-resistant crop—cassava—or

[illegible]

When planning to improve the nutrition of tropical indigenes or to correct chronic protein malnutrition, it should be noted that dried milk, stored in cans on the shelf at ambient temperatures for one year, may lose three quarters of its biological value. This loss is in amino acids—some of these acids are destroyed and others become biologically unavailable—and in certain vitamins, particularly pyridoxine. Children fed chiefly or exclusively on one of these milks

[illegible]

[illegible] during the cultivating and harvesting seasons women are required to toil in the fields with primitive and inefficient implements from early morning through the heat of the day. In some places this work is done after only a little sweetened coffee or gruel has been taken upon arising. The meal of the day is not eaten until evening. Pregnancy and lactation except for the first month or two after parturition, usually does not exempt them from this duty. In addition to the calories expended in this strenuous work, the adult in the tropics [illegible]

feasts while in others, it may be imp... to include as a staple of diet...

...fore it is eaten ... washed and cooked in water. Ranganathan *et al* found that losses from raw rice due to washing and cooking amounted to 15 per cent of the calories, 10 per cent of the protein, 75 per cent of the iron, and 56 per cent of the calcium and phosphorus,[13] while Swaminathan[14] found that up to 85 per cent of the thiamine also was lost. Although rice enrichment programs have been successful in reducing beriberi substantially in certain parts of the Philippines where this deficiency disease was prevalent, they are considered by some investigators to be impracticable for large scale application.[15]

Food plants in different parts of the world may vary considerably in biological value. Dean has noted that maize, which usually has a low lysine content and a lysine methionine ratio usually of 2:3, in Guatemala has a still lower content of methionine and the ratio accordingly is 4:2.[16] In most areas of Central America maize is not only low in lysine and methionine but is especially low in tryptophane. The deficiency of the latter amino acid accounts principally for the low biological value ...

Moreover, in the regions where total intakes of protein are low, this deficiency usually is aggravated by exceptionally low intakes of animal protein, although it is appreciated that high quality protein alone is not a substitute for an adequate quantity of total protein. In China, there is only 5 gm. of animal protein available daily per capita. This figure is matched by that of 9 gm. in India and 4 gm. in Java and Madura.[3] Similar low intakes of animal protein are the rule in many parts of Africa, Central America, and the West Indies.[6, 10, 20, 21, 22] In a survey of four Nigerian tribes, Nichols[23] calculated that one tribe—the Dakarkerri—consumed daily only 2 gm. of animal protein per capita. They offset this low intake of protein of good quality, however, by consuming a large quantity of vegetable protein, 85 gm. per capita daily. Another tribe—the Isokos—consumed only 46 gm. total of protein daily per capita, 20 gm. of which was of animal origin. Incidentally, hepatomegaly was noted in 9 per cent of the Dakarkerris and in 19 per cent of the Isokos, and 5 per cent of the former had ascariasis while 31 per cent of the latter were found to be infected with this parasite. In some parts of Africa, cattle are considered as measures of wealth and, except for special feasts, are not slaughtered for food. In many other parts of the tropics, the peasants sell the cattle and seldom use them for their own food requirements. In coastal strips and along rivers and lakes, where fish are eaten, animal protein and total protein intakes are much higher and deficiency diseases are less common.[6, 10, 11, 26, 27] In rural areas where transportation facilities are lacking, little fish is eaten except occasionally

for imported expensive salt or dried fish Pond culture of fish is being attempted in some countries to eliminate this inadequacy

In parts of the tropics the live weight of cattle does not exceed 450 to 500 lb and the output of milk during a seven to eight months lactation does not exceed 145 gal Where better supplies of milk are available peasants usually prefer to sell the milk when possible while in other regions because it is so

the infant (*vide infra*)

Dean[24] has observed also that in East Africa food habits have changed in some parts because local supplies of certain foods have become exhausted and that changes in agricultural schemes are brought about by the discovery of a new preference by necessity or by the completion of a government agricultural plan He recommends that a famine resistant crop—cassava—or

[illegible] temperatures for one year may lose three quarters of its biological value This loss is in amino acids—some of these acids are destroyed and others become biologically unavailable—and in certain vitamins particularly pyridoxine Children fed chiefly or exclusively on one of these [illegible]

[illegible] are considerably lower than estimates based on average consumption of the family or community[10] allowances should be considered for losses of nutrient content of foods during cooking[6]

In many tropical countries depending on local [illegible] sistence it is the custom of [illegible] pensable to food production [illegible] vesting seasons women are [illegible] to toil in the fields [illegible] ineffic[illegible] some [illegible] [illegible] the day is not eaten until evening Pregnancy and lactation except for the first month or two after parturition usually does not exempt them from this duty In addition to the calories expended in this strenuous work the adult in the tropics particularly when

exposed to the direct rays of the sun and sweating heavily, may lose in excess of 4 gm of nitrogen daily via the skin[16] It would be interesting to speculate on the amino acid pool nitrogen balance, and circulating proteins during work under these conditions

Although intestinal helminths and *other parasites affect young children more* severely than adults (*vide infra*), in those areas where these infections are prevalent and consequently intense, the pregnant mother may manifest not only the residual effects of such childhood infections but also those of a current helminthiasis—if severe with accentuation of the existing malnutrition

These dietary privations are further accentuated by crop failures caused by drought and by the seasonal reductions between harvests—the hungry months when *diets may be reduced to levels of less than 1 000 calories daily* —substantially below the local energy requirements particularly those of the pregnant or lactating mother The deleterious effects of such dietary privation on maternal nutrition during the hungry months or during crop failures are not limited to just these periods On the basis of observations on Africans in whom after prolonged periods of protein starvation it was found that adequate diets for at least three months were required to attain nitrogen balance[25] it is obvious that *these periods of aggravated maternal malnutrition may extend* well beyond the harvests

Diverse taboos are encountered in various countries of the tropics and although some may be beneficial many are undoubtedly detrimental to good maternal infant and child nutrition In India, according to Rao[3] dietary deficiencies are common among nursing mothers and children of even upper classes because of religious restrictions Protein of animal origin *e g* meat fish or fertilized chicken eggs is not eaten by orthodox Hindus In many regions of Africa where tribal taboos forbid mothers to eat certain fish eggs and chickens the diets are made additionally defective in protein[26] while in others the pregnant woman is allowed to eat fish[27]

Deficiency diseases of adult tropical indigenes may be latent and *only become* manifest clinically under stress Pregnancy and lactation are stress factors that in tropical women commonly accentuate and bring to light the indications of malnutrition including anemia hepatic disease edema and even cardiac insufficiency

The principal deficiency anemias of the tropics are iron deficiency, or hypochromic microcytic and megaloblastic macrocytic Iron deficiency or hypochromic microcytic anemia *may be the result of (1) insufficient* dietary iron [illegible] chronic diarrhea or

fection (disease) esophageal varices associated with schistos[illegible] cirrhosis and portal cirrhosis

These anemias occasionally are so severe especially when there is more than one *factor responsible e g hookworm* disease and pregnancy that transfusion of blood may be urgently required The majority of these anemias however will respond satisfactorily to iron therapy and an adequate intake of protein especially when the responsible factor *e g* hookworm is reduced or

eliminated. A great deal of discussion has been centered upon hookworm anemia with some investigators asserting that iron alone is sufficient to produce and maintain cure, while others contend that iron alone will not provide cure and that, in order to maintain the therapeutic effects of iron, the intake of protein must be adequate or the hookworm burden must be removed or significantly reduced.[29-37]

Megaloblastic macrocytic anemias are (1) those probably caused by the dietary lack of such extrinsic factors as folic and folinic acids, vitamin B_{12} and other B complex vitamins as well as protein[31-35] and include (a) tropical macrocytic anemia and (b) dimorphic anemia, a variant of the former due to associated iron deficiency. (2) those presumably caused by impaired absorption of extrinsic factors and include (a) anemia of sprue and (b) the anemia accompanying pellagra, which also may be due partly to a lack of extrinsic factor. *Diphyllobothrium latum* (fish tapeworm) anemia is confined chiefly to the Baltic littoral, over 70 per cent of cases being reported from Finland.[36-39]

Tropical macrocytic anemia is the term conferred by Wills on a megaloblastic anemia observed in indigenous populations of tropical and subtropical climates.[40-42] This anemia, originally considered to be associated only with pregnancy, has been found to occur in nonpregnant women as well as in men. It can be distinguished from pernicious anemia, which it closely resembles, by the fact that achlorhydria is no more frequent than it is in the rest of the local population, and spinal myelopathy does not occur. The stress of the increased nutritional requirements of pregnancy in women in whom malnutrition is latent or imminent probably may be sufficient to precipitate manifest anemia. In Costa Rica, a severe hypochromic macrocytic (dimorphic) anemia is frequently observed, and is considered to be due to malnutrition, multiple pregnancies, and hookworm disease.[44] Similar cases have been reported from Africa.[44]

Tropical hemolytic anemias, including those caused by infections such as malaria and *Bartonella* and the hypersplenism associated with kala azar and schistosomiasis (Banti's syndrome), as well as the familial hereditary sickle cell state are frequently conditioned or aggravated by protein malnutrition and iron deficiency.

In many countries, as children grow into adolescence and adulthood, they continue to maintain diets similar to those on which they previously developed kwashiorkor.[70] A high incidence of protein malnutrition in children usually indicates undernourishment and malnutrition of the general population.[48] In many instances the diets of adults are observed to be poorer in that they are deficient in calories as well as protein. Then, as a consequence of illness, infection, pregnancy, lactation, or prolonged severe exertion (long treks), acute kwashiorkor may be precipitated in the adult.[70, 45] In certain regions of South America, Central America, and the West Indies, however, the diets of adults are better qualitatively as well as quantitatively.[10-47]

Lesions of the liver with severe chronic protein malnutrition (kwashiorkor) can occur in adults (Davies[45]) and in lactating mothers.[7] These lesions resemble the fatty infiltration and necrosis, cellular infiltration and fibrosis observed in the livers of young children, although, probably as a consequence

of conditioning during acute attacks of kwashiorkor in childhood, there is a greater degree of fibrosis Pancreatic sclerosis due to periacinal, peritubular, and periductal fibrosis is observed in adults, and associated atrophy of the enzyme secreting glands of the small intestine result further in disturbed digestion and attendant impaired absorption Gillman and Gilbert[43] reported that fatty liver disease occurs much more frequently in acute pellagrins than in other members of the general population in South Africa and that, in pellagra

liver in adults is doubted, it is generally accepted that adult tropical cirrhosis, which is indistinguishable from Laennec's portal cirrhosis as observed in temperate zones is linked with chronic protein malnutrition[6, 7, 20, 45, 49, 60-53] It would appear that kwashiorkor, after it has been cured, does not inevitably lead to continuing cirrhosis if the diet remains satisfactory (in many places this is unlikely, vide supra) and cirrhogenic factors or substances are not prevalent[7, 53] There is no significant sex difference in cirrhosis of the liver as encountered in Africans[54]

The increased frequency of cirrhosis of the liver in certain tropical areas was noted many years ago Rogers[55] in 1911 reported that cirrhosis of the liver among native Indians in Ceylon was observed in 6 9 per cent of postmortem examinations and thus was seven times more frequent than cirrhosis in Eu

terial infection and toxins absorbed from bowel ulcerations were etiological factors in the production of the cirrhosis In the light of present-day knowledge, however, it is probable that chronic protein malnutrition accentuated by chronic dysentery was the basic causative factor Almost 40 years later, Fernando[51] found the incidence of cirrhosis to be still high in Ceylon (death rate for cirrhosis was 22/100,000 in Colombo (1949), and 1 95/100 000 in England and Wales) Of 192 patients with hepatic cirrhosis 24 had toxic cirrhosis and 168 had Laennec's cirrhosis It was considered that Laennec's cirrhosis, in most instances, was the consequence of malnutrition

otic cir

rhosis resulting from increased iron intake and storage under the term hemo chromatosis ' Walker and Arvidsson[60] after studying iron overload in the South African Bantus, have concluded on the basis of microscopic examination of liver tissue that iron overload in the Bantu does not lead to cirrhosis and that hemochromatosis is distinct from siderosis They point out that in sidero sis in the Bantus pancreatic pigmentation when it occurs is only slight that hepatic fibrosis is often absent that diabetes is rare and that in hemochromato sis iron storage even early is parenchymal

Anomalous serum proteins are found over most of the tropics with total serum protein values of the indigenes being the same or greater than those of their temperate zone counterparts Before modern electrophoresis techniques were used for determining the patterns of serum protein fractions some investigators sought to show that there was no close relation between malnutrition and altered serum proteins It has become evident since that total serum protein values are deceptive inasmuch as the progressive decrease in serum albumin is often coupled with an apparent compensatory increase in gamma globulin In malnutrition excluding the consideration of certain protozoan infections hy pergammaglobulinemia is thought to be due to liver damage Alterations of the serum protein with lowering of the albumin fraction have been reported from diverse parts of the tropics[10, 5, 61, 64] Although it has been decided that hypoalbuminemia and the hunger edema of Europe were not closely asso ciated it has nevertheless been considered highly probable that there is an almost invariable relation between hypoalbuminemia and edema in protein malnutrition as it occurs in the tropics[7, 20, 61, 65, 66]

Tropical ulcer and malnutrition are commonly associated in impoverished areas It is probable that the conditions leading to its development are those associated with poverty viz malnutrition dirt trauma and invasion by common skin bacteria fusiform bacilli and spirochetes The extent of the causative role of malnutrition in the development of tropical ulcer has not been determined It is recognized however that protein malnutrition materially interferes with healing In Uganda Loewenthal[67] observed that tropical ul cers did not occur in natives who consumed milk and meat Rao[5] reported that tropical ulcer was most common in those areas of India where malnutrition and anemia accentuated by malaria and hookworm were prevalent especially on the tea plantations in Assam[68] and on coffee plantations in South Africa[69] Tropical ulcer became even more prevalent during World War I when poverty and food privation worsened in Calcutta[70, 71] Poindexter[72] considered that an insufficiency of protein and vitamins was a factor in determining the chronicity of tropical ulcer In Haiti we observed that where there was a heavy seasonal rainfall malnutrition dirt trauma and infections were the principal factors that acted jointly to produce the ulcer as well as to contribute to the chronicity and extent[3] In patients with extensive chronic ulcers the malnutrition was apparently aggravated by continuous seeping of protein rich serosanguineous fluid from the base of the ulcer

Since the fetal economy is dependent on the status of maternal health the infant born of a malnourished native tropical mother is likely to be immature and under weight The tropical infant endowed with only meager resources is p

inimical environment where a succession of merciless adversaries is awaiting it Thus shortly after beginning its mundane existence, it must compete for survival where only the most tenacious can survive

An opportunity to observe the effects of maternal nutritional privation on the economy of the fetus was provided by the recent war in Europe In Wuppertal, [illegible]
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Uganda, birth weights were found to match those of European babies, whereas in the Congo, they were reported to be 400 to 500 gm less In India, birth weights of infants of malnourished mothers averaged about 700 gm less than those of babies of European mothers [6] In parts of Central America, children born at term are usually premature in appearance [41] Similar observations have been made in India and other parts of Asia where maternal malnutritional is prevalent Although it is usually impossible to ascertain the length of gestation in tropical countries, it is generally recognized that these low birth weights are not necessarily due to prematurity but rather to immaturity

Despite the fact that native tropical mothers may have lower serum albumin values than their European counterparts, the serum albumin values of African infants match those of their European contemporaries [63] The values of all of the constituents of blood serum, particularly vitamin A and carotene, were lower in newborn children in Guatemala City than those of newborn children in the United States [74]

Although anemia is usual in malnourished tropical mothers the hemoglobin values of newborn infants in East Africa are comparable to those of European newborns [75, 76] It is inconceivable that severe anemia in the woman would

reflected in the infant at birth, anemia may become manifest at a later date when deficient fetal iron stores (a result of maternal deficiency) are not adequate to hold pace with rapid growth during the first several months of life [75, 76]

Contrary to previous notions, the quality of breast milk of malnourished mothers in the tropics, except for a higher fat content in some parts of Africa compares favorably with that of their American and European counterparts Jelliffe[77] in 1952 noted that the breast milk of Nigerian mothers had an average protein content of 1 04 (range 0 59 to 1 76), despite poor diets inadequate in protein, and he confirmed similar observations made by Trowell[78] in Uganda in 1948 The breast milk of Indian mothers of the poorer class in the Nilgiris whose children were suffering from kwashiorkor, was found by Shrinivasan and Ramanathan[79] to contain 1 59 per cent of protein compared to 1 27 per cent in the breast milk of healthy mothers 30 4 mg per cent of methionine and 26 1 mg per cent of cystine, compared to 29 1 mg per cent and 19 0 mg per cent, respectively Walker, Arvidsson, and Draper[80] ascertained that the breast milk of 31 poorly nourished, 190 average, and 45 well nourished

South African Bantu mothers, eating diets based on maize, bread, and legumes did not differ materially from that of their American and European counterparts except for a lower content of vitamin C and niacin In places where beri beri is endemic the breast milk is also deficient in thiamine

Although the nutritional status of the mother is often poor, tropical infants usually continue to grow satisfactorily during the early months of breast feeding and growth weight curves are comparable to those of infants in the United States and England[7, 21, 10, 61] At six to eight months, sometimes

suitable Diarrhea which frequently results from such supplementary foods accentuates the insufficiency of the diet

roportionately higher re Dean[16] points out that ely with growth during these early months since the infant receiving an adequate quantity of breast milk will continue to grow satisfactorily although there is no corresponding increase in the available quantity of breast milk The optimal amount of protein required for satisfactory growth is not known according to Dean On the basis of temperate zone standards however the requirement of protein increases from a probable amount of 14 gm daily (supplied in 1 200 gm of breast milk) providing a protein kg ratio of about 2 1 at five to six months to 40 gm at two years to 50 to 60 gm by seven years and 70 to 90 gm thereafter in a good mixed diet with two-thirds animal protein and one third plant protein It is appreciated that in many underdeveloped countries of the tropics the daily protein intakes do not exceed 30 gm and often are no more

investigations in Central America[18, 82] based on studies on child feeding with plant protein made by Dean[83] in Germany would seem to show that an adequate quantity of protein from any source provided the intake of calories and certain vitamins is sufficient is more important than the animal protein content of the diet

Nutritional deficiencies in infancy and childhood usually become manifest at the time when the supply of breast milk is failing and supplementary feeding is begun According to Brock and Autret[7] the most serious and widespread of these nutritional disorders is kwashiorkor which is also known in various parts of the world as *sindrome policarencial infantil* *culebrilla* and except for pigmentary disturbances as *distrofia de farinacei* *dystrophie de farineuse* and probably *Mehlnährschaden* Kwashiorkor is defined as a nutritional disorder associated with a low protein diet occurring particularly during the age period between six months and five years It is apparent that the term 'protein' is not restrictive, and that the deficiency must include B

inimical environment where a succession of merciless adversaries is awaiting it Thus shortly after beginning its mundane existence, it must compete for survival where only the most tenacious can survive

An opportunity to observe the effects of maternal nutritional privation on the economy of the fetus was provided by the recent war in Europe In Wuppertal, West Germany, although average birth weights had been reduced slightly by 1939, there was a further decline of 210 gm by 1945 This reduction was not as great as that in Rome in 1944 and in Vienna in 1945, where birth weights were 400 to 500 gm less than in preceding years [24] Unfortunately, recorded birth weights are not available for much of the tropical world In parts of Uganda, birth weights were found to match those of European babies, whereas in the Congo, they were reported to be 400 to 500 gm less In India, birth weights of infants of malnourished mothers averaged about 700 gm less than those of babies of European mothers [6] In parts of Central America, children born at term are usually premature in appearance [43] Similar observations have been made in India and other parts of Asia where maternal malnutritional is prevalent. Although it is usually impossible to ascertain the length of gestation in tropical countries, it is generally recognized that these low birth weights are not necessarily due to prematurity but rather to immaturity

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Although anemia is usual in malnourished tropical mothers, the hemoglobin values of newborn infants in East Africa are comparable to those of European newborns [75, 76] It is inconceivable that severe anemia in the woman would not affect the blood of the fetus, and it is highly probable that women with very low hemoglobin values usually do not conceive but that, if they do they will abort Though a low maternal hemoglobin of the mother may not be reflected in the infant at birth, anemia may become manifest at a later date, when deficient fetal iron stores (a result of maternal deficiency) are not adequate to hold pace with rapid growth during the first several months of life [75, 76]

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Although the nutritional status of the mother is often poor, tropical infants usually continue to grow satisfactorily during the early months of breast feeding and growth weight curves are comparable to those of infants in the United States and England[7, 8, 10, 11] At six to eight months sometimes earlier, the growth of the tropical infant begins to lag behind that of the temperate zone infant indicating that there is probably an insufficiency of breast milk and that foods given to supplement the infant's diet—chiefly carbohydrate and at times, adult foods with curry and spices—are inadequate and unsuitable Diarrhea which frequently results from such supplementary foods accentuates the insufficiency of the diet

It is acknowledged that the young infant has a proportionately higher requirement for nitrogen than older children and adults Dean[14] points out that the nitrogen requirements must diminish progressively with growth during these early months since the infant receiving an adequate quantity of breast milk will continue to grow satisfactorily although there is no corresponding increase in the available quantity of breast milk The optimal amount of protein required for satisfactory growth is not known according to Dean On the basis of temperate zone standards however the requirement of protein increases from a probable amount of 14 gm daily (supplied in 1 200 gm of breast milk) providing a protein kg ratio of about 2 1 at five to six months to 40 gm at two years to 50 to 60 gm by seven years and 70 to 90 gm thereafter in a good mixed diet with two-thirds animal protein and one third plant protein It is appreciated that, in many underdeveloped countries of the

been settled whether animal protein is indispensable for growth Current investigations in Central America[14, 22] based on studies on child feeding with plant protein made by Dean[13] in Germany would seem to show that an adequate quantity of protein from any source provided the intake of calories and certain vitamins is sufficient is more important than the animal protein content of the diet

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complex vitamins, vitamin A in some areas and, possibly, vitamin C. In localities in Haiti, where kwashiorkor was prevalent, we were impressed by associated vitamin A deficiency, particularly among adults. Furthermore, the syndrome is not limited to these age groups: in Central America, cases are seen in children through 12 years[10] and, in Africa, adult cases have been reported and the pathology has been described.[45]

It has been generally accepted that kwashiorkor is the result of prolonged consumption of a diet that is deficient in protein, as well as other essential factors, and in which the proportion of animal protein is low while that of carbohydrate is usually high. Such diets have a low protein calorie ratio and a very low animal protein calorie ratio. In Central America, Autret and Behar[10] found many cases in which the calorie intake had been inadequate from an early age and in which there were manifestations of undernourishment as well as of malnutrition. In Djakarta, where rice is the mainstay of the diet and malnutrition is prevalent, Ooman[84] has observed that malignant malnutrition (kwashiorkor) is the result of a reduction of total calories and total protein with animal protein absent or minimal.

The intake of food is aggravated by anorexia and occasionally by vomiting and the digestion of food and absorption of nutrients are hampered by diarrhea. Of these three symptoms associated with the syndrome, the last named deserves special mention, since most of the children with kwashiorkor have diarrhea. In some cases, diarrhea occurs as a consequence of alteration of pancreatic and intestinal enzyme functions and must be viewed as a result of the protein deficiency. In other children, diarrhea can be ascribed to parasitic or bacterial infection or to an unsuitable diet. In the opinion of Autret and Behar,[10] parasitic and other infectious diarrheas are most common in Central America and frequently precipitate a true deficiency disease in children who already are on the verge of malnutrition.

At this stage, there is decreased utilization of food, partly due to atrophy of the acini of the pancreas and of the enzyme secreting cells of the small intestine,[84, 85] and to consequent reduction of amylase, lipase, and trypsin in the small intestine.[21, 85, 86] In children that recover but probably have additional attacks of the malnutrition syndrome, fibrosis or sclerosis of the pancreas is usual in later life. These pancreatic and intestinal lesions are coupled with atrophic changes in the parotid and lacrimal glands, and are viewed as the primary lesions of kwashiorkor.[20, 50] They are attended by the characteristic fatty infiltration of the cells of the periphery of the liver lobules, lymphocytic infiltration of the portal triads, and a thickening of the reticulum in the same part of the lobules.[45, 81] These early changes of the liver are followed by increased fatty infiltration, which progresses in a centrolobular direction, cellular necrosis, and collagenization and fibrosis of the thickened reticulum in and around the portal triads—the so called "stellate fibrosis" of Davies.[50] Davies views the "stellate fibrosis" as the stamp of kwashiorkor which, although it is not found before the weaning period, is common subsequently.

In two other widely separated regions of the tropics, other forms of nutritional liver disease occurring in infants and children have been described

serous hepatosis in Jamaica, in the West Indies, by Hill,[88] and hepatic cirrhosis in infants and young children in India and Ceylon. This cirrhosis apparently is encountered as two distinct types (1) a portal cirrhosis of the Laennec type and (2) a form of biliary cirrhosis first described by Gibbons[89] in 1891. The latter usually is rapidly progressive, commonly affecting children one to three years of age of middle and high class Hindu families. Both are frequently accompanied by jaundice and are fatal. The role of viruses and of *Escherichia coli* in the etiology of the latter is uncertain.[5, 90]

Malnutrition and infections in the tropics are inseparably linked and make up the warp and weft of the fabric of disease of many tropical indigenes.

Tropical infections contrast with those of temperate climates in so far as more of them are caused by animal parasites. Although many are caused by the same organisms that produce infections in temperate climates, resistance and susceptibility to these, as well as to animal parasites, are more profoundly influenced by environmental, ecologic and anthropological factors and by natural, racial, inherited and acquired immunity.

Even though protein malnutrition is generally accepted as the fundamental determinant in kwashiorkor and although acute bacterial or viral infection, especially pneumonia, bronchitis and diarrhea, can precipitate the syndrome, there is no unanimity of opinion regarding the role of parasitic infections. Brock and Autret[7] point out that kwashiorkor occurs among Africans in Johannesburg, the majority of whom have never been exposed to such tropical parasitisms as malaria, schistosomiasis, filariasis, leishmaniasis and ancylostomiasis. They refer to Platt and McGregor (*loc cit*) who emphasized the importance of parasitism, particularly malaria in the Gambia, and to the fact that the age of maximal incidence of kwashiorkor and the age of relative absence of immunity to malaria are the same. Brock and Autret conclude: whereas tropical parasites are probably always contributory to the etiology of kwashiorkor in the area surveyed and may sometimes play and important part, it is likely that the dietary factor is always dominant. Autret and Behar[10] in discussing the etiology of *sindrome policarencial infantil* in Central America state that while the etiological influence of intestinal parasitism may be admitted, it should be regarded as an indirect or secondary cause. They also call attention to the fact that injudicious vermifuging may precipitate the

helminths, particularly *Ascaris lumbricoides*, play a significant role in aggravating kwashiorkor in many areas of the tropics. Investigators in India have stressed the interrelation of malnutrition and infection, particularly malaria and hookworm infection.[93-97] They consider that while malnutrition predisposes to infection, infection is a conditioning factor that aggravates the nutritional deficiency. In Indonesia[2] the prevalence of hookworm disease among indigenes with indications of protein malnutrition has led to energetic programs to combat this parasitism.

Williams calls attention to the fact that ascariasis is common in many parts

of the world where kwashiorkor is found and is an important factor in a large proportion of the cases of this syndrome[93] She believes that too little attention has been directed to the devastating effects of ascariasis, and notes that one or two male *Ascaris* in the intestine of a young infant, though they may produce no eggs and therefore remain unrecognized, may create havoc in the digestive system and even cause death We think that infections with virgin female *Ascaris*, which may be more prevalent and possibly more serious than male infections, can also be missed, since their bizarre eggs either may not be recognized or are not recovered in the yields of some diagnostic techniques[98,100] Williams also points out that in areas where there is a high incidence of ascariasis, even though the adults may harbor them in apparent symbiosis, the effect of *Ascaris* on children who have not yet acquired an immunity is quite different When a child develops an acute febrile illness (*vide supra*), the ascarids often depart via the mouth nose, or rectum and, in chronic disease, they may already have left before the child is brought for examination *Ascaris*, therefore, may be a factor in a case of kwashiorkor although all the worms have departed Infections with *Ascaris* may deprive the host of nutrients by high metabolic requirements (40 per cent of dry weight is protein formed from essential amino acids and content of thiamine, niacin, pantothenic acid, pyridoxine, and vitamin B_{12} in the worm's tissues is high), secretion of trypsin inhibitor (for protection against dissolution in intestinal canal), mechanical interference by heavy worm burden, mucosal irritation and increased secretion of mucin, and, at times, fever and diarrhea

In two rural areas of Haiti, where malnutrition was prevalent, we found ...fected

In localities in Haiti, however, where vitamin A deficiency and protein malnutrition were prevalent, we found that ascariasis was uncommon and that the incidence of all intestinal helminth infections was less than 6 per cent On the other hand, we noted that intestinal protozoan infections, as well as malaria were common The incidence of *Endamoeba histolytica* infections was 45 per cent, and of *Giardia lamblia*, 33 per cent

Hookworm usually does not significantly affect the child who is younger than two years inasmuch as infants and young children are seldom exposed to infection until they crawl or toddle in spots infested with larvae Loughlin and Stoll (1946), however showed that severe and even fatal hookworm disease in young children and infants in an age group considered relatively free from infection, could be contracted from fomites[101] After hookworm disease has ... be raised by increased protein ... hookworm burdens ... increasing the need for protein for blood regeneration and by interfering with food and protein intake, may further reduce already low serum albumin levels and thereby precipitate or aggravate edema[21] Trincao *et al*,[10?] in a study of the blood proteins in cases of ancylostomiasis in Portuguese Africa, found that the blood

albumin was relatively lowered and that the gamma globulin was at least 50 per cent higher than normal The close association of hookworm and pellagra in Egypt was pointed out by Khalil,[103] who found that pellagra was six times more common in hookworm patients than in the general population, and by Robertson and Doyle,[104] who observed that 46 per cent of 300 hookworm pa

may reduce the ability of the African infant to withstand infections such as hookworm ascariasis bronchitis and pneumonia to which it is exposed In holoendemic regions Garnham[105] remarks that children almost from birth are in contact with the malarial parasite and that, apparently due to passive immunity acquired from the mother the infection rate during the first two or three months is only 10 per cent whereas half of the infants are infected by the sixth month and practically all are infected by the ninth month This apparent relative immunity in breast fed infants also may be due to an antiplasmodial effect of milk, similar to that demonstrated by Maegraith[106] in *Plasmodium berghei* infections of milk fed rodents as confirmed by others [107] The reduction in the quantity of breast milk at five to six months (*vide supra*) may be associated with this significant rise in the incidence of malarial infections at that time Since the metabolic requirements are raised by fever due to malaria as well as other infectious agents it is highly probable that latent chronic protein malnutrition can be precipitated into manifest kwashiorkor or that once established, the latter can be aggravated

Brock and Autret [7] Autret and Behar [10] and Thompson[21] have called attention to the interrelation of kwashiorkor and diarrheas of protozoan or bacterial origin Although the protozoa giving rise to diarrhea are not specified we should suppose that most cases are due to infection with *Endamoeba histolytica* *Giardia lamblia* also can cause diarrhea as well as steatorrhea and Veghelyi[108] has stressed the association of steatorrhea and impaired absorption in giardiasis

The mechanisms whereby kwashiorkor and other multiple deficiencies are precipitated by diarrhea are intricate but may be constructed as follows the hurried passage of food through the intestinal canal interferes with digestion and absorption of nutrients and results in increased loss of nutrients including B complex vitamins as well as fluid and electrolytes, anorexia limits the intake of nutrients fever associated with these infections aggravates the diminished intake and increased loss of nutrients by raising the protein vitamin C and B complex vitamin requirements intestinal irritation ulceration, and bleeding incident to the infection cause losses of fabricated protein in enzymes mucin exudate and blood the feeding of starchy diets that are still further reduced in calories aggravates all of the aforementioned factors until a severe multiple deficiency syndrome is finally reached

These views regarding the role of parasitisms in precipitating or aggravating deficiency diseases are not without experimental support Chandler,[109] on the basis of animal and human investigations, has remarked that the physiological welfare of the host as it contributes to the balance in host parasite relations,

is particularly affected by diet He considers that the diet, under certain circumstances, influences the ability of the host to develop specific immunity in infectious diseases, whether caused by bacteria, protozoa, or helminths Poor diets, particularly those deficient in protein or containing proteins of poor biological value, eventually will interfere with the production of antibodies that are modified globulin formed from essential amino acids When growth and antibody production must compete in a malnourished and parasitized young animal, both are adversely affected and, unless this is corrected by improving the quality of the diet with regard to its content of biologically good protein or by removing part or all of the parasite burden, the young animal is unable to survive because there is insufficient material to supply both

Interest in the association of parasitic infection and malnutrition has been active for many years (*vide supra*) It was astonishing, however, to find a reference by Sambon (1908) to the Ebers papyrus written in 1550 B C, in which the *āaa* disease, an endemic anemia, was ascribed to an intestinal worm—the Heltu worm[110] While, in 1906, Shipley and Fearnsides[111] remarked that it was *in children who require every gram of their food for growth that the loss* is appreciable, and that we have passed from the day since Jordens in 1803 (*loc cit*) called intestinal worms "the good angels and unfailing helpers of children"

The treatment of helminthic and protozoan infections, when they are associated with severe chronic protein malnutrition (kwashiorkor), has generally been considered as unnecessary and even dangerous until the malnutrition has been significantly improved This trend in therapy has evolved from the following premises (1) infants and young children suffering from severe malnutrition that is associated with parasitic infections, particularly ascariasis hookworm, amebiasis, and malaria, seldom tolerate commonly used parasiticides, (2) treatment of parasitic infections without simultaneous improvement of the diet does not ameliorate the manifestations of malnutrition, (3) the belief that certain deficiency diseases can be cured by merely supplying the deficient substances, *e g*, hookworm anemia "cured" by administration of iron, (4) the comparatively high percentage of cases of malnutrition in which helminthic and protozoan infections are not found at the time of examination, (5) the unavailability of efficacious nontoxic parasiticides, (6) the failure to realize that such parasitic infections intensify the effects of the deficiency of vitamins and other nutrients, that "nonspecific stress" reactions resulting from combined infection and deficiency can cause adrenal cortical changes, and produce changes in those organs with high metabolic activity, especially the small intestine and liver

The commonly used parasiticides (santonin, oil of chenopodium, carbon tetrachloride, emetine, certain 8 aminoquinolines) have low therapeutic ratios even in persons who ar [illegible] dent there
fore, that such toxic dr [illegible]
infant or young child [illegible]
and purgation are also prescribed to complete the treatment with certain anthelmintics Nevertheless, despite the introduction of new parasiticidal agents—including the broad spectrum antibiotics oxytetracycline and tetra

cycline, the piperazine compounds, and newer 4-aminoquinolines—most of the aforementioned toxic drugs are still being used in many areas either because they are readily available, are inexpensive, or because workers in the tropics are more familiar with their use

Williams[93] has remarked that although ascariasis is prevalent in parts of the world where kwashiorkor is found the ascarids already may have departed from the intestinal canal of the sick child before it is brought for examination In these cases, even though the infection may be intense enough to aggravate the dietary insufficiency or to precipitate a severe state of malnutrition, the interrelation of the parasitism and the malnutrition is generally overlooked Thus the absence of *Ascaris* in such cases does not lessen the need in other cases for treating ascariasis when it is associated with malnutrition, provided an effective and nontoxic drug is available Other severe helminthic and protozoan infections may be similarly regarded

It should be realized that, when malnutrition has resulted from dietary insufficiency accentuated by parasitism even though the depletion caused by the parasites may be severe, the entire picture of malnutrition cannot be entirely reversed by merely removing the parasites Thus treatment of the parasitism and simultaneous improvement of the diet are required to ameliorate the malnutrition Although the anemia of hookworm disease can usually be corrected by giving iron it has become evident that unless a significant part of the hookworm burden is removed the relief is only temporary and cannot be maintained after the increased intake of iron has been stopped

Tropical infections caused by metazoan protozoan and some bacterial parasites may be manifested either as chronic or as acute or fulminating diseases In these infections particularly when they are chronic and are associated with chronic malnutrition there is sufficient time for serious deficiencies of the B complex vitamins and of vitamin C to develop Although it is not generally realized, there is reason to believe also that many of these cases have progressed to a stage comparable to the exhaustion phase of the general adaptation syndrome" (Selye)[112a, b, c] It is under these conditions that the treatment of parasitic infections associated with deficiency diseases should be directed toward (1) speedily correcting the protein malnutrition and/or undernutrition (2) rapidly arresting the critical depletion by parasitic infection(s) with orally or parenterally administered efficacious nontoxic chemotherapeutic or antibiotic agents (3) correcting the depletion of thiamine, certain B complex vitamins and vitamin C that has resulted from infection as well as from dietary deficiency, and the consequent "nonspecific stress" reactions causing adrenal cortical damage, and injury to those organs with high metabolic activity especially the intestine and the liver It thus would seem to be a *sine qua non* that these vitamins should be administered simultaneously with anti infective therapy and not delayed until later when further systemic and intestinal depletion undoubtedly will have occurred

Beginning in 1950 we have had occasion to study deficiency diseases and interrelated parasitic infections in the Republic of Haiti Although Haiti is comparatively small—less than 11 000 square miles in area—deficiency diseases and parasitisms are not unvarying throughout the country Contrariwise, they

differ according to localities or regions as they might be affected by topical climatic, environmental and, possibly, by anthropological factors Consequently, it would be impossible, after surveying a few limited areas, to generalize about the diseases affecting the entire population In certain localities, chronic

prevalent, at least 75 per cent of the natives being infected In others, hookworm disease is a problem and, in still others, both of these parasites, as well as *Trichuris*, are prevalent In certain localities where chronic protein malnutrition and vitamin A deficiency are common, less than 6 per cent of the natives have these helminthiases,
and 33 per cent respective
tions of prevalence Bac
treponematoses—yaws and pinta—vary in regional prevalence or distribution In a locality where vitamin A deficiency is common, pinta is prevalent while yaws is rare Tropical ulcer also is regional in its prevalence (*vide supra*) and is found frequently in areas where yaws is prevalent Although the treatment of these diseases in Haiti obviously must be individualized according to the kind of deficiency and parasitism, the objectives outlined above, nevertheless have continued to be generally applicable Accordingly, we have treated malnutrition and/or undernutrition associated with ascariasis, hookworm, malaria, amebiasis, yaws, and tropical ulcer, and have used certain new chemotherapeutic compounds and broad spectrum antibiotics as anti infective agents

Ascariasis In the treatment of ascariasis associated with malnutrition, we have found certain piperazine compounds, including diethylcarbamazine (Hetrazan) and piperazine calcium edathamil (Perin), to be innocuous These compounds are highly effective, are available in syrups, and, with regimens of either one dose (45 mg/kg body weight) of piperazine calcium edathamil, or four single doses administered on consecutive days (each dose, 15 mg/kg) of diethylcarbamazine, up to 94 per cent of *Ascaris* are expelled These piperazines seldom cause toxic reactions, but these reactions, when they do occur, are usually mild Dietary restriction, fasting, and purgation are not required to increase their effectiveness or to diminish their toxicity[113 115]

Hookworm The piperazines are not effective in the treatment of hookworm However, Crystoids Anthelmintic (hexylresorcinol) can be given with comparative safety to children who can swallow pills Two or three doses given several days apart (0 1 gm for each year of age through 10 years to the adult

empty, it should preferably be given with water in the morning and food should be withheld for several hours Purgation is not required in the treatment of hookworm with hexylresorcinol

can be administered in single doses We have found that a single dose of hydroxychloroquine (Plaquenil) caused a prompt clinical response and a rapid disappearance of the parasitemia in falciparum malaria[116] These doses ranged from 1 0 gm for children less than six years and 1 5 gm for those between 6 and 12 years to 2 0 gm for adults A single dose of hydroxychloroquine has been found to be effective also in the treatment of vivax malaria[117] Under circumstances where oral administration is impossible, hydroxychloroquine can be administered parenterally in single doses of one sixth to one third the amount given orally

Pyrimethamine because of possible folic acid antagonism[118-120] and certain 8 aminoquinolines are not recommended for treating malaria in debilitated anemic and malnourished individuals

In a recently published paper[121] we discussed the use of the broad spectrum antibiotic oxytetracycline (Terramycin) in the treatment of some tropical diseases including amebiasis certain helminthiases the shigelloses donovanosis (granuloma inguinale) lymphopathia venerea the treponematoses—yaws and pinta—and tropical ulcer Oxytetracycline has been used in Haiti to treat amebiasis, yaws pinta tropical ulcer lymphopathia venerea donovanosis (granuloma inguinale), and certain helminthiases including enterobiasis Although the first four are commonly associated with deficiency diseases lymphopathia donovanosis and enterobiasis usually are not causally related An earlier substantial part of this program was designed to study the efficacy of oxytetracycline in the treatment of yaws amebiasis and tropical ulcer while lately the program has been expanded in its therapeutic aspects to include tetracycline (Tetracyn) and oxytetracycline and tetracycline combined with Stress Formula (SF) vitamins such as Terramycin SF and Tetracyn SF respectively

Dosage of Oxytetracycline and Tetracycline These antibiotics are usually administered orally as follows to children less than 5 years of age 1 0 gm daily to children between 5 and 10 years 1 5 gm daily to those more than 10 years and to adults 2 0 gm daily Of course the dosages are modified according to the infection being treated In amebiasis and donovanosis these doses are usually administered once daily for 10 consecutive days In yaws pinta and tropical ulcer they are given once daily for five consecutive days In enterobiasis a seven-day regimen is used and in lymphopathia venerea, a 28 day regimen is applied Under certain circumstances where parenteral administration is considered necessary oxytetracycline and tetracycline can be effectively administered by intramuscular injection in the following doses for any of the above periods or until oral administration can be instituted children less than 5 years 150 mg injected once daily children between 5 and 10 years 200 mg injected once daily children more than 10 years and adults 250 mg injected once daily

Four capsules of Terramycin SF or Tetracyn SF containing 1 0 gm of the antibiotic also supply the following amounts of water soluble Stress Formula vitamins 10 mg of thiamine 10 mg of riboflavin 100 mg of niacinamide 20 mg of calcium pantothenate 2 mg of pyridoxine 1 5 mg of folic acid 4 mcg of vitamin B_{12} 300 mg of ascorbic acid, and 2 mg of vitamin K Thus six

capsules (1 5 gm of antibiotic) will supply one and one half times the Stress Formula, and eight capsules (2 0 gm of antibiotic) will supply two times the Stress Formula

Amebiasis Oxytetracycline has been found to be a consistently superior, relatively nontoxic, safe therapeutic agent in acute amebiasis[122-125] Unlike some arsenical compounds and halogenated hydroxyquinolines, oxytetracycline is rapidly effectual in controlling diarrhea and eliminating *Endamoeba histolytica* from intestinal ulcers and the feces, and does not require preliminary control of the diarrhea with emetine to be effective Consequently, emetine, which is contraindicated in young children and is highly toxic for debilitated and malnourished individuals, need not be administered Inasmuch as oxytetracycline has been found to be more effectual than other chemotherapeutic drugs and antibiotics in the treatment of shigelloses[126] and since differential diagnosis may be impossible in areas where amebic and bacillary dysenteries are both prevalent, the use of this antibiotic is currently recommended for treating acute

In preliminary investigations of the comparative efficacy of oxytetracycline and tetracycline we find that these antibiotics have essentially the same clinical effect in amebiasis when cases are observed for periods of six weeks posttreatment As a consequence of experiments showing that a combination of equal parts of oxytetracycline and tetracycline produced a fourfold increase in inhibitory effect on *E histolytica in vitro*, over that obtained when either antibiotic was used singly,[127] we were prompted to investigate this synergism clinically In 14 patients with intestinal amebiasis thus far treated with a combination of equal parts of oxytetracycline and tetracyline—the total dose of both antibiotics being the same as when either is used singly—we have observed no relapses during six weeks posttreatment periods Inasmuch as antibiotics

tein malnutrition and they intensify the severity of the latter by fever and anorexia Malnutrition and anemia commonly accompany late yaws, particularly when fabricated protein is lost in the serosanguineous fluid that seeps from large ulcerous lesions or when destructive lesions involving the oral cavity interfere with nutrition Oxytetracycline, administered either orally or parenterally has been found to be highly efficacious in the treatment of both late and early yaws[128-132] The rapid response of early yaws to oxytetracycline

and face (gangosa) deforming osteoperiostitis, gummas and extensive ulc lesions of the extremities is arrested with one or two and, occasionally, courses of oxytetracycline therapy as outlined above Treatment of

lesions of late yaws with oxytetracycline not only directly improves the nutrition of the individual but also improves the physical condition of the adults so that they can again become productive members of the community Although we have observed Jarisch Herxheimer reactions, particularly in infants and young children treated with procaine penicillin, we have not encountered

malnutrition The fact that such reactions do not occur with oxytetracycline therapy is especially important when considering the treatment of yaws associated with latent malnutrition or with manifest kwashiorkor

Tropical ulcer (phagedenic ulcer) We previously have indicated that the treatment of tropical ulcer should comprise systemic as well as local measures [21] The former included a diet high in calories high in protein content and having supplements of B complex vitamins and vitamin A Antimicrobial therapy systemically administered was considered optional but in Haiti, where yaws

to the base and margins of the ulcer It was noted that acute ulcers reacted

within six to eight weeks Those patients with very extensive ulcers that had failed to heal completely with this therapy nevertheless were sufficiently improved to be able to return home and resume gainful work

Terramycin SF and Tetracyn SF The comparative efficacy of oxytetracycline and tetracycline when administered singly or simultaneously in the same capsules with stress formula vitamins is being currently investigated in amebiasis yaws pinta tropical ulcer donovanosis lymphopathia venerea and certain helminthiases As noted before amebiasis yaws pinta and tropical ulcer in Haiti are commonly associated with deficiency states malnutrition and/or undernutrition These antibiotics—oxytetracycline and tetracycline

Although the numbers of cases of individual diseases treated with oxytetracycline alone tetracycline alone oxytetracycline with stress formula vitamins and tetracycline with stress formula vitamins are still too few to draw more

advantages of Terramycin SF and Tetracyn SF are factual advantages (1) ulcerous lesions of late yaws and tropical ulcer when treated with these antibiotic stress formula combinations manifestly heal more rapidly than when

capsules (1 5 gm of antibiotic) will supply one and one half times the Stress Formula, and eight capsules (2 0 gm of antibiotic) will supply two times the Stress Formula

Amebiasis Oxytetracycline has been found to be a consistently superior, relatively nontoxic, safe therapeutic agent in acute amebiasis[1??,124] Unlike some arsenical compounds and halogenated hydroxyquinolines, oxytetracycline is rapidly effectual in controlling diarrhea and eliminating *Endamoeba histolytica* from intestinal ulcers and the feces, and does not require preliminary control of the diarrhea with emetine to be effective Consequently, emetine, which is contraindicated in young children and is highly toxic for debilitated and mal nourished individuals, need not be administered Inasmuch as oxytetracycline *has been found to be more effectual than other* chemotherapeutic drugs and antibiotics in the treatment of shigelloses[1?6] and, since differential diagnosis may be impossible in areas where amebic and bacillary dysenteries are both prevalent, the use of this antibiotic is currently recommended for treating acute infectious diarrheas associated with chronic protein malnutrition (kwashiorkor) Recent short term observations in South Africa have disclosed that tetracycline may be as effective as oxytetracycline in the treatment of acute amebiasis[124] In preliminary investigations of the comparative efficacy of oxytetracycline and tetracycline, we find that these antibiotics have essentially the same clinical effect in amebiasis when cases are observed for periods of six weeks post treatment As a consequence of experiments showing that a combination of equal parts of oxytetracycline and tetracycline produced a fourfold increase in inhibitory effect on *E histolytica, in vitro*, over that obtained when either anti biotic w

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antibiotics being the same as when either is used singly—we have observed *no* relapses during six weeks' posttreatment periods Inasmuch as antibiotics have little beneficial effect on hepatic amebiasis (hepatitis and abscess), chloroquine (not emetine) is the recommended drug, particularly for malnourished and debilitated adults, and for infants and young children

Yaws The early lesions of yaws frequently are associated with chronic protein malnutrition, and they intensify the severity of the latter by fever and anorexia Malnutrition and anemia commonly accompany late yaws, particularly when fabricated protein is lost in the serosanguineous fluid that seeps from large ulcerous lesions or when destructive lesions involving the oral cavity interfere with nutrition Oxytetracycline, administered either orally

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surface lesions, as determined by phase microscopy, and a remarkable improvement of appetite *The progress of destructive lesions of the oral cavity* and face (gangosa), deforming osteoperiostitis, gummas, and extensive ulcerous lesions of the extremities is arrested with one or two and, occasionally, three courses of oxytetracycline therapy as outlined above Treatment of these

lesions of late yaws with oxytetracycline not only directly improves the nutrition of the individual, but also improves the physical condition of the adults so that they can again become productive members of the community Although we have observed Jarisch Herxheimer reactions, particularly in infants and young children treated with procaine penicillin, we have not encountered such reactions from oxytetracycline therapy We have seen such reactions, when they are accompanied by a sharp febrile response and anorexia precipitate a severe deficiency state or aggravate an already manifest chronic protein malnutrition The fact that such reactions do not occur with oxytetracycline therapy is especially important when considering the treatment of yaws associated with latent malnutrition or with manifest kwashiorkor

Tropical ulcer (phagedenic ulcer) We previously have indicated that the treatment of tropical ulcer should comprise systemic as well as local measures [12] The former included a diet high in calories high in protein content and having supplements of B complex vitamins and vitamin A Antimicrobial therapy systemically administered was considered optional but in Haiti where yaws is endemic oxytetracycline was administered according to the dosages used in the treatment of late yaws Since ulcerous lesions of late yaws had responded so favorably to topically applied oxytetracycline systemic therapy was supplemented with daily topical applications of crystalline oxytetracycline to the base and margins of the ulcer It was noted that acute ulcers reacted promptly to combined oxytetracycline therapy and to improved diet and that healing was complete within two or three weeks Chronic ulcers however were notably slower in their response with half of the ulcers healing completely within six to eight weeks Those patients with very extensive ulcers that had failed to heal completely with this therapy nevertheless were sufficiently improved to be able to return home and resume gainful work

Terramycin SF and Tetracyn SF The comparative efficacy of oxytetracycline and tetracycline when administered singly or simultaneously in the same capsules with stress formula vitamins is being currently investigated in amebiasis yaws pinta tropical ulcer donovanosis lymphopathia venerea and certain helminthiases As noted before amebiasis yaws pinta and tropical ulcer in Haiti are commonly associated with deficiency states malnutrition and or undernutrition These antibiotics—oxytetracycline and tetracycline when supplied in the same capsules with stress formula vitamins have made it possible to determine whether there are definite advantages to administering the required and or previously deficient vitamins at exactly the same moment as the antibiotics

Although the numbers of cases of individual diseases treated with oxytetracycline alone tetracycline alone oxytetracycline with stress formula vitamins and tetracycline with stress formula vitamins are still too few to draw more than generalized conclusions it might be possible nevertheless to extrapolate *from the total number of cases of all the diseases treated thus far Preliminary* observations disclose that what were considered initially as hypothetical advantages of Terramycin SF and Tetracyn SF are factual advantages (1) *ulcerous lesions of late yaws and tropical ulcer when treated with these anti*biotic stress formula combinations manifestly heal more rapidly than when

only the antibiotics are administered (2) ulcerous lesions of the large intestine

either antibiotic to individuals with deficiency diseases associated with infection provide a safe balanced combination of these essential substances—a fact that may be critically important in the treatment of infections when they are associated with kwashiorkor (4) the stress formula vitamins exhibit no patent inhibitory effects on the antiparasitic activity of either antibiotic when they are used to treat the aforementioned infections (5) the absence of notable toxic reactions in 134 cases of bacterial protozoan and metazoan infections treated with Terramycin SF and Tetracyn SF in New York N Y, as well as in Haiti is noteworthy (6) there is no apparent difference in the antimicrobial activity of either Terramycin SF and Tetracyn SF

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Discussion of the Paper

Doctor Norman R Stoll (*Rockefeller Institute of Medical Research New York, N Y*) To a parasitologist obviously there were many things in Doctor Loughlin's paper which are of interest I want to raise a point for Bailey K Ashford in connection with hookworm You remember that hookworm which is an infection related to trematodiasis was described by Bilharz in Egypt about 100 years ago and about 10 years later by Wucherer in Brazil The great interest the medical world took in this disease occurred somewhat later first in the late 1870 s following the construction of the Simplon Tunnel in Europe and the miners anemia that spread from it and then in the late 1890 s, with the discovery that anemia in Puerto Rico was essentially a hook worm anemia It was soon determined that the degree of severity of this disease—and it took about three decades to make this decision—was related to the number of worms that the individual had That made it very simple People with small numbers of worms had little manifestation of disease Darling with large numbers of worms had a great deal of such manifestation went so far as to say that the degree of depression of hemoglobin had a linear relation to the number of worms As he said 100 worms represented such and such depression of hemoglobin Having clarified the problem in this way we then discovered that there were people who theoretically should have had but did not have very deep anemias These cases occurred particularly in certain areas A general correlation of the theory was obtainable in some parts of the world but not in others This difficulty puzzled the hookworm workers a great deal The discrepancy was ascribed to race It was ascribed more recently to the development of the experimental pattern of immunities a word we never used in connection with worm diseases until about 20 years ago The difficulty was ascribed particularly to bad nutrition by Ashford and due to the emphasis he put on the idea I think you would forgive me if I quote a few sentences from his autobiography* published in 1934 the year of his death Ashford states For the benefit of intelligent readers both lay and professional both here and abroad we amply acknowledge the very important place taken by nutritional unbalance in producing the picture recognized all over Puerto Rico as *la anemia* or in other words hookworm disease But the undeniable fact remains that this was not a nutritional but a parasitic anemia That it was capable of cure and of prevention by specific drugs and the use of latrines respectively is seen from the history of the sensational transformation of a helpless anemic at death s door to a ruddy vigorous laborer simply on the expulsion of these tiny worms and without any alteration in his accustomed food How then does the influence of poor diet come in? Thus parasites plus poorly balanced food bring fatalities and serious grades of anemia which

* Ashford B K 1934 A Soldier in Science Morrow & Co New York N Y

ld not o cur from paras tes alone Onl ho e er hen the f d

Puerto Ricans and much more meat It is therefore no longer a medical problem but a sociologic one of the very first water'

NUTRITIONAL DISORDERS IN BILHARZIAL CASES WITH HEPATOSPLENIC AFFECTION

By A. H. MOUSA, A. EL MOFTY, M. KHATTAB, A. EL DEEB AND M. HASHEM

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ova of *Bilharzia* deposited in portal tracts. Parenchymatous changes occur in these formations very late (FIGURE 1a).

Although most Egyptian peasants do not consume alcohol, they are frequently subject to nutritional-deficiency diseases, as their staple diet consists of carbohydrate, mostly maize, and their deficiency is conditioned by a heavy parasitism and by chronic intestinal infections accompanied by intermittent or prolonged diarrhea. Their nutritional deficiency is also precipitated or aggravated by hepatotoxic and antibacterial drugs used indiscriminately for treatment (FIGURE 2).

It seems that patients with hepatic bilharziasis are vulnerable to virus hepatitis, becoming infected enterally or parenterally during the course of antibilharzial treatment (FIGURES 3a, b and c). Such multiple etiological factors lead to a complicated type of cirrhosis in addition to the predominant bilharzial one.

A unique opportunity was seized to study the nutritional aspects of three types of hepatic fibrosis and cirrhosis in a group of 96 patients living on the same diet and in the same environment. The etiology of hepatic disorders as based on histopathological grounds[1] was predominantly parasitic in 40 per cent, nutritional in 32 per cent, and viral in 28 per cent, all having urinary or intestinal types of bilharzial infestation or both.

In all of the cases studied, special stress was placed on the nutritional deficiency disorders as manifested clinically, biochemically, and radiologically. In addition, histopathological changes in the liver were studied through needle biopsies.

Cases in the *predominantly nutritional group* were characterized by:

(1) High incidence of residual and *recurrent* symptoms of pellagra (80 per cent), endemic parotitis, a few cases having enlarged lacrimals as well, ariboflavinosis without circumcorneal injection, and vitamin A deficiency. Peripheral neuritis was noted in most of these cases (FIGURE 4a).

(2) Frequency of moderate and severe anemia or prolonged diarrhea.

(3) Higher incidence of hepatomegaly with smaller spleens; in only 5 per cent a shrunken right lobe of the liver with moderately enlarged spleen was noted.

(4) Early appearance of anasarca affecting both upper and lower extremities and an effusion in one side of the pleural cavity.

(5) Higher incidence of endocrinal imbalance in the form of dwarfism in

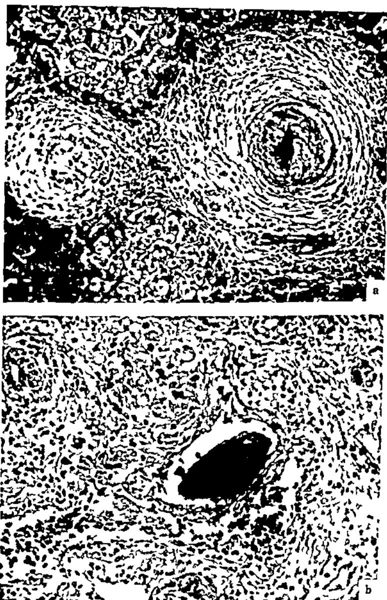


FIGURE 1 (a) Bilharzial periportal fibrosis (b) Bilharzia ova in a portal tract High magnification

antilism, alopecia of the trunk and pubic areas, as well as unilateral or bilateral gynecomastia[2] (FIGURES 4b, c, and d) In one case, gynecomastia became more apparent after Fuadin treatment administered in the hospital

(6) In two cases, hypervolemia was noted, with engorged neck veins in the absence of congestive heart failure or emphysema

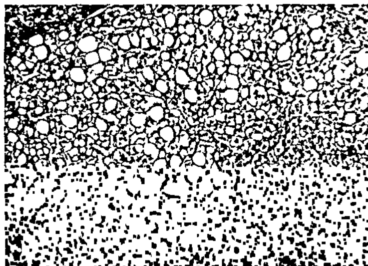


FIGURE 2 Nutritional fatty infiltration in a bilharzial liver

(7) Minimal symptoms and signs of portal hypertension whether manifested by dyspepsia, hematemesis, or dilated abdominal veins

Biochemically and radiologically, the nutritional group showed

(1) A higher incidence of hypoalbuminemia and a low hemoglobin percentage conditions that are easily corrected by diet The dysproteinemia could be differentiated in three groups, as shown in TABLE 1

(2) Liver functions are less affected in the viral group and simulate their condition in the late stages of hepatic bilharziasis They showed mild hypoglycemia with relative insulin resistance, indicating earlier impairment of the carbohydrate function of the liver[2] (FIGURE 5)

(3) The 17 ketosteroids were found low in all cases, while the effect of adrenaline and of the ACTH test on eosinophils excluded primary hypoadrenalism[3] Estrogenic inactivation is dependent on the availability of the vitamin B complex and so is markedly more deficient in this group than in the other two groups

(4) No hyperbilirubinemia was met with, a condition that is constant in the viral group and terminal in some of the bilharzial groups

(5) Ascitic fluid is low in protein content and specific gravity, as well as in cellular count which contrasts with the higher figures for both in the other two groups

(6) Hypochlorhydria, which responds to histamine, and deficient pancreatic juices,[4] as examined by a modified Miller Abbot tube after injection with Prostigmin,[4] are higher in incidence than the other groups They show marked improvement after prolonged dietetic therapy, especially when vitamin A is included



FIGURE 3 (a) Postinfective hepatitis cirrhosis in a case of bilharziasis

(7) A percutaneous lienohepatography[4] showed milder grades of portal vein dilation and kinking of the splenic vein (FIGURES 6a and b) Visualized collaterals, however, were not met with in this group, while the intrahepatic portal venules were constantly filled,[5] a condition seen in late bilharzial cases[6] The portal circulation time is not differential, as the presence of collaterals compensates for the delay in cases with portal hypertension Hiatus hernia was found in the chronic ascitic forms of the three groups (FIGURE 7a)

(8) The intestinal pattern, although slightly affected in the three groups was more apparent in the nutritional cases[3] with a return to normal in the cases followed (FIGURE 8), affecting mainly the junction of the jejunum with the ileum

(9) Steatorrhea was mild and infrequent, but no case of megalocytic anemia was met with in either group

(10) The incidence of toxic jaundice after Diodotrast injection during the recording of lienohepatographies was found[5] to be commoner in cases with parenchymal liver damage

Summary and discussion The findings described above clarified variations in the clinical picture and the course of endemic hepatic bilharziasis among



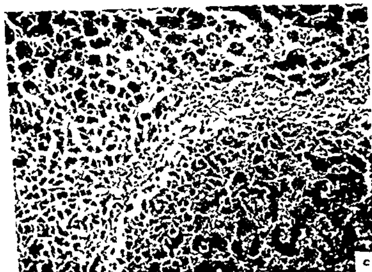


FIGURE 3 (b) Post [illegible] hepatitis cirrhosis in a case of bilharziasis (c) Acute hepatic necrosis with hemorrhage in a bilharzial case (viral hepatitis)

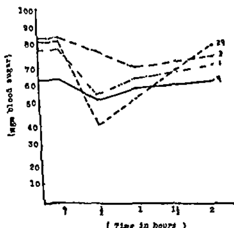
[illegible] fatal risks when treated collectively with antibilharzial or common anthelmintic drugs It must be borne in mind that [illegible]



FIGURE 4 (a) Endemic parotitis with enlarged lacrimals (b) Gynecomastia developed during antibilharzial treatment (c and d) Gynecomastia in hepatomegaly predominantly of postnutritional type

TABLE I

Blood protein	Parasitic	Viral	Nutritional
Albumin	± Normal	Diminished (*not easily cor*rected by diet)	Diminished (easily corrected by diet)
α Globulin	++	−−	−−
β Globulin	±	±	±
γ Globulin	++++	++	++



An example of insulin sensitive (29) and three examples of relative insulin resistant curves.

FIGURE 5 Fasting hypoglycemia with insulin resistance and delayed return to normal in hepatic bilharziasis with nutritional deficiency diseases compared to a normal control (dashed curve)



FIGURE 6 (a) Liver hepatography in bilharzial cases.



FIGURE 6 (b) Liver hepatography in nutritional cases (c) Nonvisualized portal venules in liver of bilharzial cases Collaterals are seen

million peasants are so treated yearly in Egypt in accordance with the obligatory scheme of the antibilharzial campaign

In cases having clinical nutritional deficiency diseases with viral or bilharzial liver, the absence of fatty hepatic changes could be explained as follows (1) the diet may be deficient in certain vitamins, but sufficient in lipotropic factors, (2) a lack of nicotinic acid may block transformation of choline into betaine thus blocking the transmethylation function of choline but accentuating its lipotropic function and (3) a substarvation diet, as in cases with prolonged diarrhea is less apt to induce hepatosteatosis than a partially deficient diet

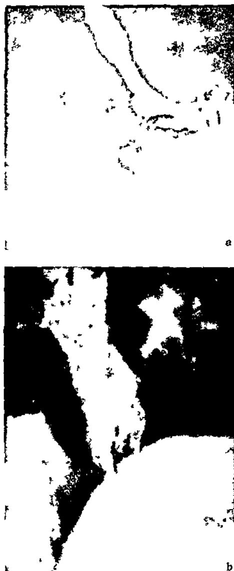


FIGURE 7 (a) Hiatus hernia (b) Esophageal varix in a bilharzial case

In conclusion, the above studied cases could be grouped nutritionally as cases in which (1) nutritional deficiency was the chief cause of liver involvement, (2) hepatic involvement incapacitated the patient economically and placed him on a lower nutritional rating, (3) hepatic disease or portal hyper



FIGURE 8 Diminished ileo-jejunal pattern

tension interfered seriously with digestion and absorption (4) the liver, as the heart of the metabolic processes showed the effect of acute or chronic injury in its nutritional function

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ALTERED PROGNOSIS IN THE DIABETIC WITH INFECTION

By Herbert Pollack
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Elsewhere in this monograph Doctor Jonathan Evans Rhoads has presented an excellent discussion on the problems concerned with nutrition in relation to infection to surgical convalescence and to other clinical aspects of nutritional disease as seen in hospitals Most of the work that he has presented was based upon experimental work both in humans and in animals

We have in our medical practice a naturally occurring classical example of this relationship of nutritional disturbance to susceptibility to infection i e diabetes mellitus Little attention has been paid to this interpretation of these phenomena by virtue of the acceptance of traditional authority The other aspect of the problem of the relation of infection to metabolism is dramatically presented in every case of ketotic acidosis precipitated by an infection This is a vicious cycle which must be understood

Many readers will recall that before insulin and even in the early insulin era when regular insulin was first introduced statements were made that increased concentration of sugar in the tissues was the cause for the severity and frequency of infections This was dictum This we accepted and nobody questioned it The professor said so and that is the way it went The introduction of regular insulin enabled us to control the blood sugar levels to some extent This limited control of blood sugar concentration did not make very much difference in the frequency and severity of infections Carbuncles if you will recall were very common in the days of regular insulin Death rate from sepsis was high in spite of the fact we could control the ketosis and acidosis associated with the infection The mortality rates ran as high as 50 per cent With the introduction of protamine zinc insulin however the whole picture has changed The long acting insulins have completely altered the prognosis of the infection in the diabetic As a matter of fact whether or not the patient has glycosuria or rigidly controls the glycosuria the immediate effect of the long acting insulins is essentially the same We know that these people on the so called free diet or free glycosuria group frequently have blood levels up to 300 mg per cent with glycosurias in the order of 100 gm a day as shown by Tolstoi in his excellently controlled series Even in Tolstoi s group

did occur it was quite severe The typical type of tuberculosis in the diabetic in the preinsulin and early insulin era was the so-called galloping consumption

tic hormones and the destruction of insulin in the body, interference with glycogen supply and a whole host of hypotheses that were purported to show why diabetics were so susceptible did not explain this

With the introduction of the long acting insulins and with a much better understanding of the whole problem of nutritional status today, we can I believe, interpret at least clinically if not experimentally, some of these facts One of the major differences between the action of the protomine zinc insulins and water soluble insulins is to maintain positive nitrogen balance even in the face of extensive glycosuria This is the key to the difference If you will recall some of the early work which was done by Wilder Boothby Atchley and Loeb in decontrolled diabetics, one of the major facts they all observed was the loss in protein that occurred with decontrol We repeated this work in our own metabolism ward and were able to show that the nitrogen losses within the first few hours after the precipitation of even a minor ketotic episode could be as much as 11 gm of nitrogen in a few hours Obviously this represents a tremendous protein dept ... insulin ... the cc ... regular use of protamine zinc exists ... In the diurnal variations in ... 24 hours ... the positive nitrogen balance with short acting insulin this phenomenon does not exist When the diabetic is treated exclusively and the concomitant negative nitrogen balance frequently develops in the long over night period and is detected in the early morning urines The ketosis disappears during the day under the influence of the injected insulin and reappears during the night when the effect of the last dose of insulin has been dissipated That meant there were periods of decontrol and period of control With the long action insulins we no longer ... and hence no diurnal period ... is m ... w ... fo ... ha ...

... discussion of infections ... esoteric solutions that role of the antibiotics Once infection has developed ... would be complete without recognition of the biotics play the same role as in the ... acting ... c ... nti ... ng ... At ... The ... It has been demo ... of insulin ... diabetes ... to some extent bolic rate ... physiolo ... its use

... ted Obviously a ... saving treatment was better than a well fed dead one When insulin was introduced it was used in connection with these minimal diets The anxieties associated with the process of learning to use insulin most efficiently resulted in the retention in use of these minimal diets As time went along and experience and con

fidence in the use of insulin was gained larger and larger amounts of food were prescribed The basic concept of undernutrition however persisted The attention of the physician was so sharply focused on the control of the carbo hydrate phase of the condition that he frequently lost track of the over all contents of the diet and the state of nutrition of his patient It was easier to control glycosuria with limited food intakes than with expanded diets Furthermore the majority of patients being treated for diabetes in the early insulin days were elderly people whose requirements as will be pointed out later

It is axiomatic that good health is dependent on optimum nutrition In order for the individual to have a sense of well being and be able to carry out his daily work the food intake must assure an adequate supply of nutrients from calories to trace elements Variations in the body s ability to store certain of these essentials lead to a necessary margin between minimal daily requirements and actual recommendations In addition one must provide for increased needs in times of metabolic stress The diabetic as is well known is peculiarly subject to these metabolic stress periods The problem is to set up recommended allowances of nutrients for the diabetic and to educate the physician in their use This will insure greater resistance to infection

RECAPITULATION AND PROSPECTS

By Howard A Schneider
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Nature, to be commanded, must be obeyed

—FRANCIS BACON

Seven years have passed since a conference was held in the United States on the topic of nutrition and infection On that occasion, at a meeting held in Minneapolis, Minn , by the Society of American Bacteriologists, emphasis was placed on the [illegible]

what different and more heterogeneous base, concerned less with experiments and weighted more with clinical experiences and epidemiological concerns I think it is also fair to say that this conference itself was an experiment, almost a "preliminary experiment" And, like an experiment, it was the test of an hypothesis that, in turn, rested on certain assumptions Now, no one in these papers has explicitly said that this was so, and my mention of assumptions is an uninvited assumption in itself I find this necessary, however, in order to epitomize the rather heterogeneous contents of the papers presented here

That the papers presented are a heterogeneous lot is, I think, almost an historical necessity, for it is now more obvious than ever that there is no clear and simple connection between infection and nutrition that has won universal assent Certainly the experimenters were aware of this lack of assent before beginning their work and, now that we have studied their reports, assent is lacking still At best, I am afraid, we have made but a beginning

A moment ago, I spoke of an unspoken hypothesis that brought us together for a fresh wrestle with this recurring hope and problem I think that the working hypothesis in these papers has been that, by a re-examination of the

re examination Unfortunately, no matter how meticulous this examination might be, it does not necessarily follow that a meaningful connection with another discipline, the study of infectious disease, is thereby established No, like so much else in science, we are confronted with an *ad hoc* necessity of searching for *evidence* of the supposed connection between nutrition and infection On such an occasion, plausibility is not enough, the construction of possible and labyrinthine connections is not enough, only proof will suffice

The strategic basis of modern nutrition rests on the operational consequences of the differences between plethora and deficit in the nutritional environment The experimenter arranges these differences, the clinician and epidemiologist assess them as they make their appearance in the natural world With few exceptions, the contributors to this monograph have leaned toward the view

* Clark, P F *et al* 1949 Bacteriol Rvs 13 99

that in striving for an abundance, in the nutritional sense, we are on the side of the angels, and that, when we come to contemplate the consequences for infectious disease of this abundance, only the happy end of an increased resistance confronts us Now, as experimenters in this field have been aware, this just is not so For example, students of infectious disease have long recognized that in viral diseases it is only the well nourished host which has maximal susceptibility, and it is the malnourished host which has an enhanced resistance The nutritionist must realize that it is an inadequate view to consider the host as a fortress, staving off infectious invaders, and that nutrition can strengthen the metaphorical walls, heighten the towers, and reinforce the garrison To believe this would be to fall into the anthropocentricity that students of infectious disease have long abandoned If nutritionists wish to make an effective contact with the study of infection, they must recognize that the reasons are clear and cogent for regarding infectious disease as an open ecological system in which the opportunistic forces of evolution lead infectious agents to occupy, frequently only temporarily, the ecological niches which the hosts provide The satisfactory nature of this ecological niche is thus equated with susceptibility, and nutrition, then, is as positively implicated in susceptibility as it is implicated in these papers with resistance

I think there is one more hidden assumption implicit in many of the papers presented here This is the silent acceptance of the myth of panresistance, the idea that "resistance to infection" is a status embracing resistance to *all* infections That this has been shown to be not only a myth, but an incorrect myth, we owe to the geneticists who have clearly demonstrated, by inbreeding and selection, that it is possible to assemble into one and the same host susceptibility to one disease and resistance to a second This means that it must be anticipated that in relating nutrition to infection there must be introduced some notions of specificity, *i e*, specific nutrients must be examined in relation to specific infections In my view, the papers in this monograph do not adequately reflect this necessity

So much for general comments Let us now turn to some of the papers themselves Among those addressed to the effect of nutrition *on* infection, I think five call for more than general comment Doctor Hill's paper on high vitamin levels and the resistance of chicks to fowl typhoid is illustrative of the difficulties in experimentation in the field of nutrition and natural resistance to infection The variance encountered in experiments of this kind demands a more complete statistical analysis than he has provided As his successive experiments show, more analysis is needed of the variance *within* his experimental groups before we are justified in placing any reliance on the differences *between* groups Indeed, in some of the later experiments some of the original differences have not been duplicated, or are reversed

The paper of Doctor Rhoads on the association between hypoproteinemia and postoperative infections is an interesting attempt to probe clinically the ideas of Doctor Paul Cannon, so frequently alluded to by many speakers at the conference Doctor Rhoads is on sound ground it seems to me, when he points to the necessity of adequate restoration of protein in the surgical patient for good surgical reasons I concur also in his reluctance, however, to conclude

that the higher incidence of infectious *complications is causally related to re* duced protein concentrations Now that Doctor Rhoads has led the way, we may expect some definitive studies on the matter It is to be hoped that such studies will be designed to test directly the effects of various protein intakes *that are referable to purified protein, such as casein, in order to avoid the* ambiguity of concomitant variations in the intake of other, unknown sub stances

The protein question leads naturally to the question of antibodies Doctor Axelrod's thoughtful paper, by restricting his analysis to specific nutritional entities and to specific antigenic processes, has made a specific and important contribution If, as Doctor Axelrod has beautifully demonstrated, some of the vitamins are involved in antibody biosynthesis, one is tempted to inquire (1) whether this is an effect on the kinetics of antibody formation and deficient animals are merely slowed, but not stopped, and (2) whether deficiencies at levels liable to be encountered in human populations are likely to affect antibody synthesis significantly Doctor Axelrod is of course, quite correct in caution ing against a too facile transposition of his results into terms of the actual in fectious disease Indeed, it may well be that his methods may find their most important use in the understanding of the intricate processes of protein syn thesis

In addition to considering the effect of nutrition on infection, there has also been some consideration of the effect of infection on nutritional status It would appear, from the papers presented here, that in the prolonged episodes of parasitic infestations (infections?) the burden of disease increases some of the nutritional demands of the host Doctor Suzman's discussion brought forward some interesting data on the precipitation of nutritional deficiency signs by infectious episodes It is apparent that the whole subject needs more in vestigation

No modern discussion of infection can be complete without consideration of the antibiotics As the paper of Doctor Milberg and Doctor Michael points out, the prolonged use of antibiotics is not without nutritional hazard due to diarrhea and anorexia It would seem that the clinician would best insure that these drains are compensated The alleged effect of such supplementation in reducing the incidence of undesirable adverse effects of antibiotic therapy is in doubt

The participants in this conference are indebted to Doctor Kinsell for a

lems *These nutritional problems of electrolyte balance, protein catabo-* *etc* are probably best met head on, as nutritional problems in themselves *But in all* candor, we still lack evidence that the nutritional manipulations thus un dertaken enable us to enter by the back door, so to speak, and that these manipulations *by indirection via the mimicry* of those end effects of the endo crines, which are presently known affect the issues of susceptibility and resistance to infection

It has probably struck the reader, as I am sure it has the participants that

in striking out to encompass the subject of these papers in its outline some details here and there have been lost from sight This may well be true If this has occurred it is probably due to the fact that when nutrition seeks to effect a junction with the problems of infectious disease it must take into account the fact that the field of infectious diseases has a well established system of values a hierarchial order of procedures that are recognized as important and effective ways of coping with infection High in this hierarchy for example are vaccination chemotherapy and antibiosis On the face of things as they are now it must be admitted that nutrition finds a lower and lesser place in this hierarchy

Indeed as our knowledge of nutrition and metabolism has grown we have been struck by the growing interrelatedness between its various items in the

think we shall also be aware that value judgments will have to be made and we shall insist on separating the demonstrable and important from the demonstrable but trivial

In this search for valid bases of our value judgments I think that nutritionists would do well to recall the great lesson now receding in the history of their science That lesson of 40 years ago was that nutrition was not then and may never be a closed deductively formulated science Forty years ago chemists wrestled with the problem of a diet supporting life and growth and found the solution to their problem not in quantiative manipulation of the items they knew but in an appeal to the natural world for new qualitatively important items the vitamins Lest we commit the same blunder and the ultimate nutritional heresy let us be aware that nutrition embraces the whole world of natural foods and let us remember that there may lie in wait for us new nutritional entities that if we but properly seek them out may well be the real bridge into the world of infectious disease Let us at least ask the question

Finally in such a clouded crystal ball as lies before us in these pages I think

waters